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(54) Title: ARYL UREAS WITH ANGIOGENESIS INHIBITING ACTIVITY

(57) Abstract: This invention relates to methods of using aryl ureas to treat diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes.



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ARYL UREAS WITH ANGIOGENESIS INHIBITING ACTIVITY

Field of the Invention

5 This invention relates to methods of treating diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes.

Background of the Invention

10 Vasculogenesis involves the *de novo* formation of blood vessels from endothelial cell precursors or angioblasts. The first vascular structures in the embryo are formed by vasculogenesis. Angiogenesis involves the development of capillaries from existing blood vessels, and is the principle mechanism by which organs, such as the brain and the kidney are vascularized. While vasculogenesis is restricted to embryonic development, angiogenesis can occur in the adult, for example during
15 pregnancy, the female cycle, or wound healing.

One major regulator of angiogenesis and vasculogenesis in both embryonic development and some angiogenic-dependent diseases is vascular endothelial growth factor (VEGF; also called vascular permeability factor, VPF). VEGF represents a
20 family of isoforms of mitogens existing in homodimeric forms due to alternative RNA splicing. The VEGF isoforms are highly specific for vascular endothelial cells (for reviews, see: Farrara et al. *Endocr. Rev.* **1992**, *13*, 18; Neufeld et al. *FASEB J.* **1999**, *13*, 9).

25 VEGF expression is induced by hypoxia (Shweiki et al. *Nature* **1992**, *359*, 843), as well as by a variety of cytokines and growth factors, such as interleukin-1, interleukin-6, epidermal growth factor and transforming growth factor- α and - β .

To date VEGF and the VEGF family members have been reported to bind to
30 one or more of three transmembrane receptor tyrosine kinases (Mustonen et al. *J. Cell Biol.*, **1995**, *129*, 895), VEGF receptor-1 (also known as flt-1 (fms-like tyrosine kinase-1)), VEGFR-2 (also known as kinase insert domain containing receptor

(KDR); the murine analogue of KDR is known as fetal liver kinase-1 (flk-1)), and VEGFR-3 (also known as flt-4). KDR and flt-1 have been shown to have different signal transduction properties (Waltenberger et al. *J. Biol. Chem.* **1994**, 269, 26988); Park et al. *Oncogene* **1995**, 10, 135). Thus, KDR undergoes strong ligand-dependant tyrosine phosphorylation in intact cells, whereas flt-1 displays a weak response. Thus, binding to KDR is a critical requirement for induction of the full spectrum of VEGF-mediated biological responses.

In vivo, VEGF plays a central role in vasculogenesis, and induces angiogenesis and permeabilization of blood vessels. Deregulated VEGF expression contributes to the development of a number of diseases that are characterized by abnormal angiogenesis and/or hyperpermeability processes. Regulation of the VEGF-mediated signal transduction cascade will therefore provide a useful mode for control of abnormal angiogenesis and/or hyperpermeability processes.

Angiogenesis is regarded as an absolute prerequisite for growth of tumors beyond about 1-2 mm. Oxygen and nutrients may be supplied to cells in tumor smaller than this limit through diffusion. However, every tumor is dependent on angiogenesis for continued growth after it has reached a certain size. Tumorigenic cells within hypoxic regions of tumors respond by stimulation of VEGF production, which triggers activation of quiescent endothelial cells to stimulate new blood vessel formation. (Shweiki et al. *Proc. Nat'l. Acad. Sci.*, **1995**, 92, 768). In addition, VEGF production in tumor regions where there is no angiogenesis may proceed through the ras signal transduction pathway (Grugel et al. *J. Biol. Chem.*, **1995**, 270, 25915; Rak et al. *Cancer Res.* **1995**, 55, 4575). In situ hybridization studies have demonstrated VEGF mRNA is strongly upregulated in a wide variety of human tumors, including lung (Mattern et al. *Br. J. Cancer* **1996**, 73, 931), thyroid (Viglietto et al. *Oncogene* **1995**, 11, 1569), breast (Brown et al. *Human Pathol.* **1995**, 26, 86), gastrointestinal tract (Brown et al. *Cancer Res.* **1993**, 53, 4727; Suzuki et al. *Cancer Res.* **1996**, 56, 3004), kidney and bladder (Brown et al. *Am. J. Pathol.* **1993**, 143I, 1255), ovary (Olson et al. *Cancer Res.* **1994**, 54, 1255), and cervical (Guidi et al. *J. Nat'l Cancer Inst.* **1995**, 87, 12137) carcinomas, as well as angiosarcoma (Hashimoto et al. *Lab.*

Invest. **1995**, 73, 859) and several intracranial tumors (Plate et al. *Nature* **1992**, 359, 845; Phillips et al. *Int. J. Oncol.* **1993**, 2, 913; Berkman et al. *J. Clin. Invest.*, **1993**, 91, 153). Neutralizing monoclonal antibodies to KDR have been shown to be efficacious in blocking tumor angiogenesis (Kim et al. *Nature* **1993**, 362, 841; Rockwell et al. *Mol. Cell. Differ.* **1995**, 3, 315).

Over expression of VEGF, for example under conditions of extreme hypoxia, can lead to intraocular angiogenesis, resulting in hyperproliferation of blood vessels, leading eventually to blindness. Such a cascade of events has been observed for a number of retinopathies, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity (Aiello et al. *New Engl. J. Med.* **1994**, 331, 1480; Peer et al. *Lab. Invest.* **1995**, 72, 638), and age-related macular degeneration (AMD; see, Lopez et al. *Invest. Ophthalmol. Vis. Sci.* **1996**, 37, 855).

In rheumatoid arthritis (RA), the in-growth of vascular pannus may be mediated by production of angiogenic factors. Levels of immunoreactive VEGF are high in the synovial fluid of RA patients, while VEGF levels were low in the synovial fluid of patients with other forms of arthritis or with degenerative joint disease (Koch et al. *J. Immunol.* **1994**, 152, 4149). The angiogenesis inhibitor AGM-170 has been shown to prevent neovascularization of the joint in the rat collagen arthritis model (Peacock et al. *J. Exper. Med.* **1992**, 175, 1135).

Increased VEGF expression has also been shown in psoriatic skin, as well as bullous disorders associated with subepidermal blister formation, such as bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis (Brown et al. *J. Invest. Dermatol.* **1995**, 104, 744).

Because inhibition of KDR leads to inhibition of VEGF-mediated angiogenesis and permeabilization, KDR inhibitors will be useful in treatment of diseases characterized by abnormal angiogenesis and/or hyperpermeability processes, including the above listed diseases

Summary of the Invention

The present invention provides a method for treating diseases in humans or other mammals which are mediated by the VEGF induced signal transduction pathway, including those characterized by abnormal angiogenesis or hyperpermeability processes. These methods comprise administering a compound of formula I below or a salt, prodrug or stereoisomer thereof to a human or other mammal with a disease characterized by abnormal angiogenesis or hyperpermeability processes.

The compounds of formula I, which include all stereoisomeric forms (both isolated and in mixtures) salts thereof and prodrugs thereof are collectively referred to herein as the "compounds of the invention."

Formula I is as follows:



wherein A is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro; and

(iv) 8 to 10 membered bicyclic heteroaryl group in which the first ring is bonded to the NH of Figure I and contains 1-3 heteroatoms independently selected from the group consisting of O, N, and S, and the second ring is fused to the first ring using 3 to 4 carbon atoms. The bicyclic heteroaryl group is optionally substituted with
5 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro.

B is selected from the group consisting of

10 (i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1 - C_5 linear or branched alkyl, C_1 - C_5 linear or branched haloalkyl, C_1 - C_3 alkoxy, hydroxy, amino, C_1 - C_3 alkylamino, C_1 - C_6 dialkylamino, halogen, cyano, and nitro;

15 (ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1 - C_5 linear or branched alkyl, C_1 - C_5 linear or branched haloalkyl, C_1 - C_3 alkoxy, hydroxy, amino, C_1 - C_3 alkylamino, C_1 - C_6 dialkylamino, halogen, cyano, and nitro;

20 (iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1 - C_5 linear or branched alkyl, C_1 - C_5 linear or branched haloalkyl, C_1 - C_3 alkoxy, hydroxy, amino, C_1 - C_3 alkylamino, C_1 - C_6 dialkylamino, halogen, cyano, and nitro;
25 and

(iv) 8 to 10 membered bicyclic heteroaryl groups having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1 - C_5 linear or branched alkyl, C_1 - C_5 linear or branched haloalkyl, C_1 - C_3 alkoxy, hydroxy, amino, C_1 - C_3 alkylamino, C_1 - C_6 dialkylamino, halogen, cyano, and nitro.
30

L is selected from the group consisting of :

- (a) $-(CH_2)_m-O-(CH_2)_l-$,
- (b) $-(CH_2)_m-(CH_2)_l-$,
- (c) $-(CH_2)_m-C(O)-(CH_2)_l-$,
- 5 (d) $-(CH_2)_m-NR^3-(CH_2)_l-$,
- (e) $-(CH_2)_m-NR^3C(O)-(CH_2)_l-$,
- (f) $-(CH_2)_m-S-(CH_2)_l-$,
- (g) $-(CH_2)_m-C(O)NR^3-(CH_2)_l-$,
- (h) $-(CH_2)_m-CF_2-(CH_2)_l-$,
- 10 (i) $-(CH_2)_m-CCl_2-(CH_2)_l-$,
- (j) $-(CH_2)_m-CHF-(CH_2)_l-$,
- (k) $-(CH_2)_m-CH(OH)-(CH_2)_l-$;
- (l) $-(CH_2)_m-C \equiv C-(CH_2)_l-$;
- (m) $-(CH_2)_m-C=C-(CH_2)_l-$; and
- 15 (n) a single bond, where m and l are 0.;
- (o) $-(CH_2)_m-CR^4R^5-(CH_2)_l-$;

The variables m and l are integers independently selected from 0-4.

M is selected from the group consisting of :

- 20 (i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;
- (ii) naphthyl, optionally substituted with 1-3 substituents independently
25 selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;
- (iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms
30 independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$,

$\text{NR}^1\text{C(O)R}^2$, $\text{NR}^1\text{C(O)OR}^2$, halogen, cyano and nitro and also oxides (e.g. $=\text{O}$, $-\text{O}^-$ or $-\text{OH}$); and

(iv) 8 to 10 membered bicyclic heteroaryl groups, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, C(O)R^1 , C(O)OR^1 , $\text{C(O)NR}^1\text{R}^2$, $\text{NR}^1\text{C(O)R}^2$, $\text{NR}^1\text{C(O)OR}^2$, halogen, cyano and nitro and also oxides (e.g. $=\text{O}$, $-\text{O}^-$ or $-\text{OH}$).

(v) saturated and partially saturated C_3 - C_6 monocyclic carbocyclic moiety optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, C(O)R^1 , C(O)OR^1 , $\text{C(O)NR}^1\text{R}^2$, $\text{NR}^1\text{C(O)R}^2$, $\text{NR}^1\text{C(O)OR}^2$, halogen, cyano and, nitro;

(vi) saturated and partially saturated C_8 - C_{10} bicyclic carbocyclic moiety, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, C(O)R^1 , C(O)OR^1 , $\text{C(O)NR}^1\text{R}^2$, $\text{NR}^1\text{C(O)R}^2$, $\text{NR}^1\text{C(O)OR}^2$, halogen, cyano and nitro;

(vii) saturated and partially saturated 5 and 6 membered monocyclic heterocyclic moiety, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, C(O)R^1 , C(O)OR^1 , $\text{C(O)NR}^1\text{R}^2$, $\text{NR}^1\text{C(O)R}^2$, $\text{NR}^1\text{C(O)OR}^2$, halogen, cyano and nitro, and also oxides (e.g. $=\text{O}$, $-\text{O}^-$ or $-\text{OH}$); and

(viii) saturated and partially saturated 8 to 10 membered bicyclic heterocyclic moiety, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, C(O)R^1 , C(O)OR^1 , $\text{C(O)NR}^1\text{R}^2$, $\text{NR}^1\text{C(O)R}^2$, $\text{NR}^1\text{C(O)OR}^2$, halogen, cyano and nitro, and also oxides (e.g. $=\text{O}$, $-\text{O}^-$ or $-\text{OH}$).

Each R^1 - R^5 are independently selected from the group consisting of:

(a) hydrogen,

(b) C₁-C₆ alkyl, preferably, C₁-C₅ linear, branched, or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo;

(c) phenyl;

(d) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S;

(e) C₁-C₃ alkyl-phenyl wherein said alkyl moiety is optionally substituted with halogen up to per-halo; and

(f) C₁-C₃ alkyl-heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said heteroaryl group is a 5-6 membered monocyclic heteroaryl or a 8-10 membered bicyclic heteroaryl, and wherein said alkyl moiety is optionally substituted with halogen up to per-halo.

Each R¹ - R⁵, when not hydrogen is optionally substituted with 1-3 substituents independently selected from the group consisting of C₁-C₅ linear branched or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo, C₁-C₃ alkoxy, wherein said alkoxy is optionally substituted with halogen up to per-halo, hydroxy, amino, C₁-C₃ alkylamino, C₂-C₆ dialkylamino, halogen, cyano, and nitro;

Each variable q is independently selected from 0, 1, or 2.

Suitable substituted and unsubstituted heteroaryl groups for the compounds of this invention, such as those for A, B and M of formula I, include, but are not limited to the following monocyclic heteroaryl groups:

2- and 3-furyl, 2- and 3-thienyl, 2- and 4-triazinyl, 1-, 2- and 3-pyrrolyl, 1-, 2-, 4- and 5-imidazolyl, 1-, 3-, 4- and 5-pyrazolyl, 2-, 4- and 5-oxazolyl, 3-, 4- and 5-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 2-, 3- and 4-pyridyl, 2-, 4-, 5- and 6-pyrimidinyl, 1,2,3-triazol-1-, -4- and -5-yl, 1,2,4-triazol-1-, -3- and -5-yl, 1- and 5-tetrazolyl, 1,2,3-oxadiazol-4- and -5-yl, 1,2,4-oxadiazol-3- and -5-yl, 1,3,4-thiadiazol-2- and -5-yl, 1,2,4-oxadiazol-3- and -5-yl, 1,3,4-thiadiazol-2- and -5-yl,

1,3,4-thiadiazol-3- and -5-yl, 1,2,3-thiadiazol-4- and -5-yl, 2-, 3-, 4-, 5- and 6-2H-thiopyranyl, 2-, 3- and 4-4H-thiopyranyl, 3- and 4-pyridazinyl, 2-,3-pyrazinyl,

and bicyclic heteroaryl groups such as :

5 Benzofuryl, benzothienyl, indolyl, benzimidazolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benz-1,3-oxadiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydrobenzofuryl, pyrazolo[3,4-b]pyrimidinyl, purinyl, benzodiazine, pterindinyl, pyrrolo[2,3-b]pyridinyl, pyrazolo[3,4-b]pyridinyl, oxazo[4,5-b]pyridinyl, imidazo[4,5-b]pyridinyl, cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, 10 cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridiazine, cyclohexanopyridazine, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene.

15 Suitable aryl groups which do not contain heteroatoms include, for example, phenyl and 1- and 2-naphthyl, tetrahydronaphthyl, indanyl, indenyl, benzocyclobutanyl, benzocycloheptanyl and benzocycloheptenyl.

20 Suitable linear alkyl groups and alkyl portions of groups, e.g., alkoxy, alkylphenyl and alkylheteroaryl etc. throughout include methyl, ethyl, propyl, butyl, pentyl, etc. Suitable branched alkyl groups include all branched isomers such as isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, etc.

25 Suitable halogen groups include F, Cl, Br, and/or I, from one to per-substitution (i.e. all H atoms on a group replaced by a halogen atom) being possible where an alkyl group is substituted by halogen, mixed substitution of halogen atom types also being possible on a given moiety. Preferred halogens are Cl, Br and F.

30 The term "up to perhalo substituted linear and branched alkyl," includes alkyl groups having one alkyl hydrogen replaced with halogen, alkyl groups wherein all hydrogens are replaced with halogen, alkyl groups wherein more than one but less than all hydrogens are replaced by halogen and alkyl groups having alkyl hydrogens replaced by halogen and other substituents.

The term "cycloalkyl", as used herein, refers to cyclic structures having 3-8 members in the ring such as cyclopropyl, cyclobutyl and cyclopentyl and cyclic structures having 3-8 members with alkyl substituents such that, for example, "C₃ cycloalkyl" includes methyl substituted cyclopropyl groups.

The term "saturated carbocyclic moieties" defines only the cyclic structure, i.e. cyclopentyl, cyclohexyl, etc. Any alkyl substitution on these cyclic structures is specifically identified.

Saturated monocyclic and bicyclic carbocyclic moieties include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and decahydronaphthalene.

Partially saturated monocyclic and bicyclic carbocyclic moieties include cyclopentenyl, cyclohexenyl, cyclohexadienyl and tetrahydronaphthalene.

Saturated monocyclic and bicyclic heterocyclic moieties include tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolane, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, piperidinonyl, tetrahydropyrimidonyl, pentamethylene sulfide and tetramethylene sulfide.

Partially saturated monocyclic and bicyclic heterocyclic moieties include dihydropyranyl, dihydrofuranyl, dihydrothienyl, dihydropiperidinyl, and dihydropyrimidonyl.

A subclass of compounds of this invention is defined by formula I, wherein A B and M are selected from phenyl, naphthyl, furyl, isoindolinyl, oxadiazolyl, oxazolyl, isooxazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiadiazolyl, thiazolyl and thienyl and are optionally substituted as defined above.

Preferred substituents for B include methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br and F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino as well as the structure
5 -L-M.

Preferred substituents for A and M include methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, *tert*-butyl, sec-butyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br and F, cyano, nitro,
10 hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino and further include:

phenyl, pyridinyl, pyrimidinyl, chlorophenyl, dichlorophenyl, bromophenyl, dibromophenyl, chloropyridinyl, bromopyridinyl, dichloropyridinyl, dibromopyridinyl, methylphenyl, methylpyridinyl, quinolinyl, isoquinolinyl, isoindolinyl, pyrazinyl,
15 pyridazinyl, pyrrolinyl, imidazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, benzopyridinyl, benzothiazolyl,

C₁-C₅ acyl;

NH(C₁-C₅ alkyl, phenyl or pyridinyl), such as aminophenyl;

N(C₁-C₅ alkyl)(C₁-C₅ alkyl, phenyl or pyridinyl), such as diethylamino and
20 dimethyl amino;

S(O)_q (C₁-C₅ alkyl); such as methanesulfonyl;

S(O)_q H;

SO₂NH₂;

SO₂NH(C₁-C₅ alkyl);

SO₂N(C₁-C₅ alkyl)(C₁-C₅ alkyl);

NHSO₂(C₁-C₅ alkyl); N(C₁-C₃ alkyl) SO₂(C₁-C₅ alkyl);

CO(C₁-C₆ alkyl or phenyl);

C(O)H;

C(O)O(C₁-C₆ alkyl or phenyl), such as C(O)OCH₃, -C(O)OCH₂CH₃,

30 C(O)OCH₂CH₂CH₃;

C(O)OH;

C(O)NH₂ (carbamoyl);

C(O)NH(C₁-C₆ alkyl or phenyl), such as N-methylethyl carbamoyl, N-methyl carbamoyl, N-ethylcarbamoyl, or N-dimethylamino ethyl carbamoyl;

C(O)N(C₁-C₆ alkyl or phenyl)(C₁-C₆ alkyl, phenyl or pyridinyl), such as N-dimethyl carbamoyl;

5 C(N(C₁-C₅ alkyl))(C₁-C₅ alkyl);

NHC(O)(C₁-C₆ alkyl or phenyl) and

N(C₁-C₅ alkyl)C(O)(C₁-C₅ alkyl).

Each of the above substituents is optionally partially or fully halogenated, such as difluoromethyl sulfonyl.

10

An embodiment of this invention includes the administration of compounds of this invention wherein in formula I, A, B and M follow one of the following of combinations:

15 A= phenyl, B=phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= phenyl, B=pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=phenyl, B = naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

20 A=pyridinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

25 A=pyridinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=isoquinolinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= isoquinolinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

30 A= isoquinolinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= quinolinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= quinolinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

5 A= quinolinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present.

The structure L of formula I is preferably -O-, a single bond, -S-, -NH-, -N(CH₃)-, -NHCH₂-, -NC₂H₄-, -CH₂-, -C(O)-, -CH(OH)-, -NHC(O)N(CH₃)CH₂-, -N(CH₃)C(O)N(CH₃)CH₂-, -CH₂C(O)N(CH₃)-, -C(O)N(CH₃)CH₂-, -NHC(O)-, -N(CH₃)C(O)-, -C(O)N(CH₃)-, -C(O)NH-, -CH₂O-, -CH₂S-, -CH₂N(CH₃)-, -OCH₂-, -CHF-, -CF₂-, -CCl₂-, -S-CH₂-, and -N(CH₃)CH₂-.

15 One of ordinary skill in the art will recognize that some of the compounds of Formula (I) can exist in different geometrical isomeric forms. A number of the compounds of Formula I possess asymmetric carbons and can therefore exist in racemic and optically active forms as well as in the form of racemic or non-racemic mixtures thereof, and in the form of diastereomers and diastereomeric mixtures. All of these compounds, including *cis* isomers, *trans* isomers, diastereomeric mixtures, 20 racemates, non-racemic mixtures of enantiomers, substantially pure, and pure enantiomers, are considered to be within the scope of the present invention and are collectively referred to when reference is made to compounds of this invention.

25 Methods of separation of enantiomeric and diastereomeric mixtures are well known to one skilled in the art. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their 30 individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or

fractional crystallization. The optically active bases or acids are liberated from the separated diastereomeric salts.

Another process for separation of optical isomers involves the use of a chiral chromatography column (e.g., chiral HPLC columns) optimally chosen to maximize the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ. The optically active compounds of Formula (I) can likewise be obtained by utilizing optically active starting materials.

The present invention encompasses any isolated racemic or optically active form of compounds described in Formula I which possess angiogenesis inhibitory activity. The term stereoisomer is understood to encompass diastereoisomers, enantiomers, geometric isomers, etc. Herein, substantially pure enantiomers is intended to mean that no more than 5% w/w of the corresponding opposite enantiomer is present.

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Salts are especially the pharmaceutically acceptable salts of compounds of formula (I) or such as, for example, organic or inorganic acid addition salts of compounds of formula (I). Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid and hydrobromic acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid, propionic acid, octanoic acid, decanoic acid, trifluoroacetic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ -aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetylaminoacetic acid, N-acetylaspargine or N-acetylcysteine), pyruvic acid, acetoacetic acid,

methanesulfonic acid, tri-fluoromethane sulfonic acid, 4-toluene sulfonic acid, benzenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, phosphoserine, and 2- or 3-glycerophosphoric acid.

5 In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of
10 triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The formation of prodrugs is well known in the art in order to enhance the
15 properties of the parent compound; such properties include solubility, absorption, biostability and release time (see "*Pharmaceutical Dosage Form and Drug Delivery Systems*" (Sixth Edition), edited by Ansel et al., published by Williams & Wilkins, pages 27-29, (1995) which is hereby incorporated by reference). Commonly used prodrugs of the disclosed oxazolyl-phenyl-2,4-diamino-pyrimidine compounds are
20 designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., pub. by
25 McGraw-Hill, pages 11-13, (1996), which is hereby incorporated by reference).

The invention also relates to methods for treating and preventing diseases, for example, angiogenesis disorders in mammals by administering a compound of this
30 invention or a pharmaceutical composition comprising one or more compounds of this invention.

A compound according to the invention can be administered simultaneously with another angiogenesis inhibiting agent to a patient with such a disorder, in the same formulation or, more typically in separate formulations and, often, using different administration routes. Administration can also be sequentially, in any order.

5

A compound according to the invention can be administered in tandem with another angiogenesis inhibiting agent, wherein a compound according to the invention can be administered to a patient once or more per day for up to 28 consecutive days with the concurrent or intermittent administration of another angiogenesis inhibiting agent over the same total time period.

10

A compound according to the invention can be administered to a patient at an oral, intravenous, intramuscular, subcutaneous, or parenteral dosage which can range from about 0.1 to about 200 mg/kg of total body weight and the additional angiogenesis inhibiting agent can be administered to a patient at an intravenous, intramuscular, subcutaneous, or parenteral dosage which can range from about 0.1 mg to 200 mg/kg of patient body weight.

15

An embodiment of the present invention is a method for treating diseases in humans and/or other mammals which are mediated by the VEGF induced signal transduction pathway which comprises administering a compound of this invention to a human or other mammal.

20

Another embodiment of this invention is a method for treating diseases in humans and/or other mammals which are characterized by abnormal angiogenesis or hyperpermeability processes with a compound of this invention to a human or other mammal.

25

Another embodiment of this invention is a method for treating diseases in humans and/or other mammals which are characterized by abnormal angiogenesis or hyperpermeability processes, which are not raf-mediated, which comprises administering a compound of this invention to a human or other mammal.

30

Another embodiment of this invention is a method for treating diseases in humans and/or other mammals which are characterized by abnormal angiogenesis or hyperpermiability processes, which are not raf mediated or p38-mediated, which comprises administering a compound of this invention to a human or other mammal.

5

Another embodiment of this invention is a method for treating diseases in humans and/or other mammals which are characterized by abnormal angiogenesis or hyperpermiability processes, which are raf-mediated and/or p38 mediated, which comprises administering a compound of this invention to a human or other mammal.

10

Another embodiment of this invention is a method for treating one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity and age related macular degeneration; rheumatoid arthritis, psoriasis, or bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis, which comprises administering a compound of this invention to a human or other mammal with one or more of these conditions.

15

Another embodiment of this invention is a method for treating one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis in combination with another condition selected from the group consisting of:

20

rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent

25

30

diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelation and oligodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement. This method comprises administering a compound of this invention to a human or other mammal with one of the above combinations of conditions.

Another embodiment of this invention is a method for treating one or more of the following conditions in humans and/or other mammals:

tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis,

in combination with an infectious disease selected from the group consisting of:

tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV). These methods comprise administering a compound of this invention to a human or other mammal with a combination of one of the above infectious diseases and one of the above diseases characterized by abnormal angiogenesis or hyperpermeability processes.

This invention further relates to kits comprising separate doses of the two mentioned chemotherapeutic agents in separate containers. The combinations of angiogenesis inhibiting agents can also be formed in vivo, e.g., in a patient's body.

5 These angiogenesis inhibiting agents can be administered in the conventional formulations and regimens in which they are known for use alone.

10 Conditions within a human or other mammal which can be treated by administering a compound of this invention are those characterized by abnormal angiogenesis or hyperpermeability processes. Conditions to be treated include tumor growth, retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity and age related macular degeneration; rheumatoid arthritis, psoriasis, or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

15 Methods of interest include the treatment of combinations of the conditions above (tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis) and another
20 condition selected from the group consisting of:

25 rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent
30 diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple sclerosis), advanced

cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and
5 allograft rejections of kidney; liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement.

Also provided is a method for treating combinations of the conditions above (tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion,
10 retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis) and an infectious disease selected from the group consisting of:

15 tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enterotoxin A resulting from *Staphylococcus* infection, meningococcal infection, and infections from *Borrelia burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's
20 encephalomyelitis virus, and the human immunodeficiency virus (HIV).

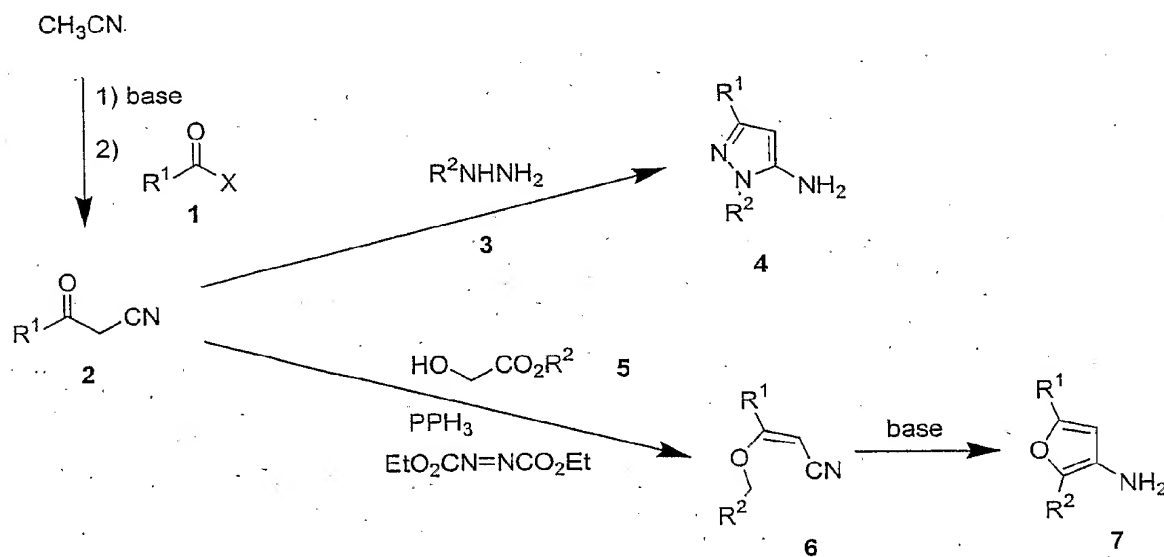
The compounds of this invention can be made according to conventional chemical methods, and/or as disclosed below, from starting materials which are either commercially available or producible according to routine, conventional chemical
25 methods. General methods for the preparation of the compounds are given below, and the preparation of a suitable compound is specifically illustrated in the Examples.

Ureas of formula (I) can be prepared by a variety of simple methods known in the art. General approaches for the formation of those compounds can be found in
30 "*Advanced Organic Chemistry*", by J. March, *John Wiley and Sons*, 1985 and in "*Comprehensive Organic Transformations*", by R. C. Larock, *VCH Publishers*, 1989), which are hereby incorporated by reference. Nevertheless, the following

general preparative methods are presented to aid one of skill in the art in synthesizing these compounds, with more detailed examples being presented in the experimental section describing the working examples.

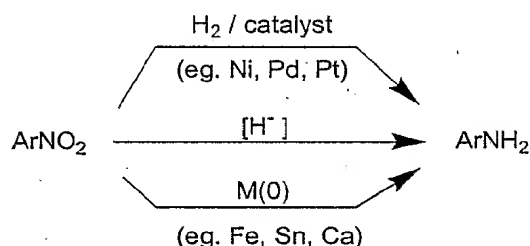
5 General Preparative Methods

Heterocyclic amines may be synthesized utilizing known methodology (Katritzky, et al. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, UK (1984). March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985)). For example, as shown in Scheme I, 5-aminopyrazoles substituted at the *N*-1 position with either aryl or heteroaryl moieties may be synthesized by the reaction of an α -cyanoketone (**2**) with the appropriate aryl- or heteroaryl hydrazine (**3**, R^2 =aryl or heteroaryl). Cyanoketone **2**, in turn, is available from the reaction of acetamidate ion with an appropriate acyl derivative, such as an ester, an acid halide, or an acid anhydride. In cases where the R^2 moiety offers suitable anion stabilization, 2-aryl- and 2-heteroarylfurans may be synthesized from a Mitsunobu reaction of cyanoketone **2** with alcohol **5**, followed by base catalyzed cyclization of enol ether **6** to give furylamine **7**.



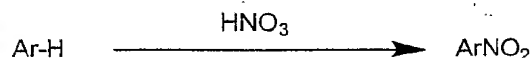
Scheme I. Selected General Methods for Heterocyclic Amine Synthesis

Substituted anilines may be generated using standard methods (March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985). Larock. *Comprehensive Organic Transformations*; VCH Publishers: New York (1989)). As shown in Scheme II, aryl amines are commonly synthesized by reduction of nitroaryls using a metal catalyst, such as Ni, Pd, or Pt, and H₂ or a hydride transfer agent, such as formate, cyclohexadiene, or a borohydride (Rylander. *Hydrogenation Methods*; Academic Press: London, UK (1985)). Nitroaryls may also be directly reduced using a strong hydride source, such as LiAlH₄ (Seyden-Penne. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH Publishers: New York (1991)), or using a zero valent metal, such as Fe, Sn or Ca, often in acidic media. Many methods exist for the synthesis of nitroaryls (March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985). Larock. *Comprehensive Organic Transformations*; VCH Publishers: New York (1989)).

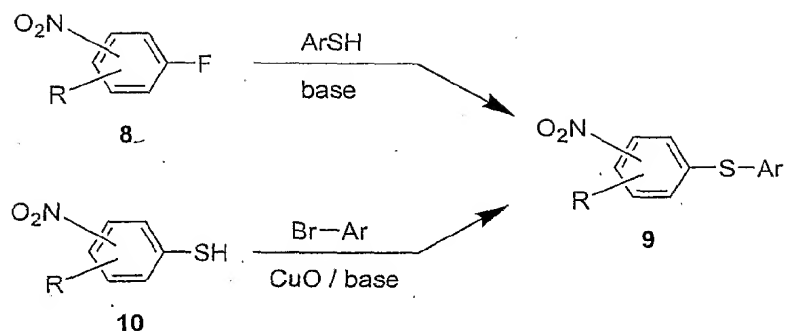


Scheme II Reduction of Nitroaryls to Aryl Amines

Nitroaryls are commonly formed by electrophilic aromatic nitration using HNO₃, or an alternative NO₂⁺ source. Nitro aryls may be further elaborated prior to reduction. Thus, nitroaryls substituted with

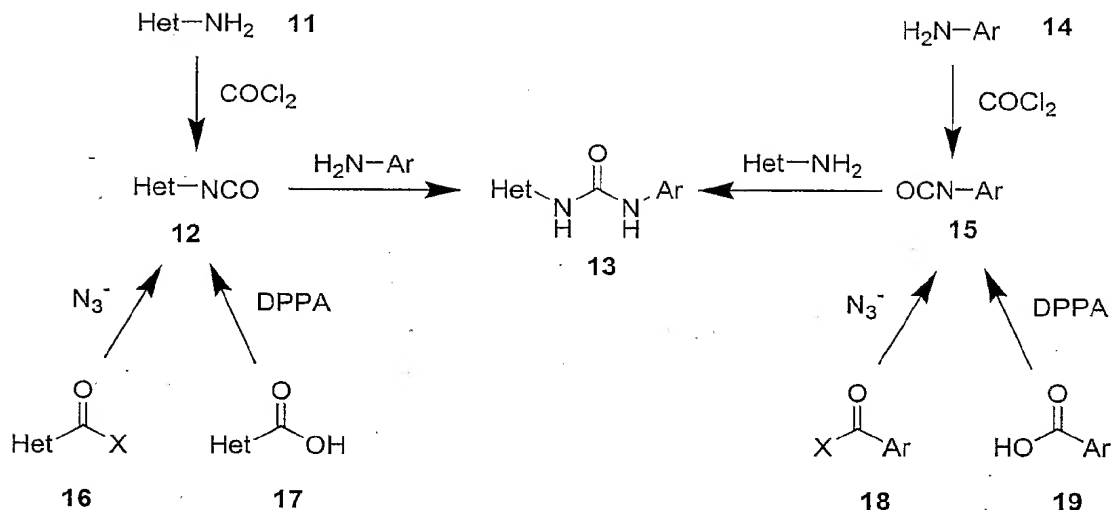


potential leaving groups (eg. F, Cl, Br, etc.) may undergo substitution reactions on treatment with nucleophiles, such as thiolate (exemplified in Scheme III) or phenoxide. Nitroaryls may also undergo Ullman-type coupling reactions (Scheme III).



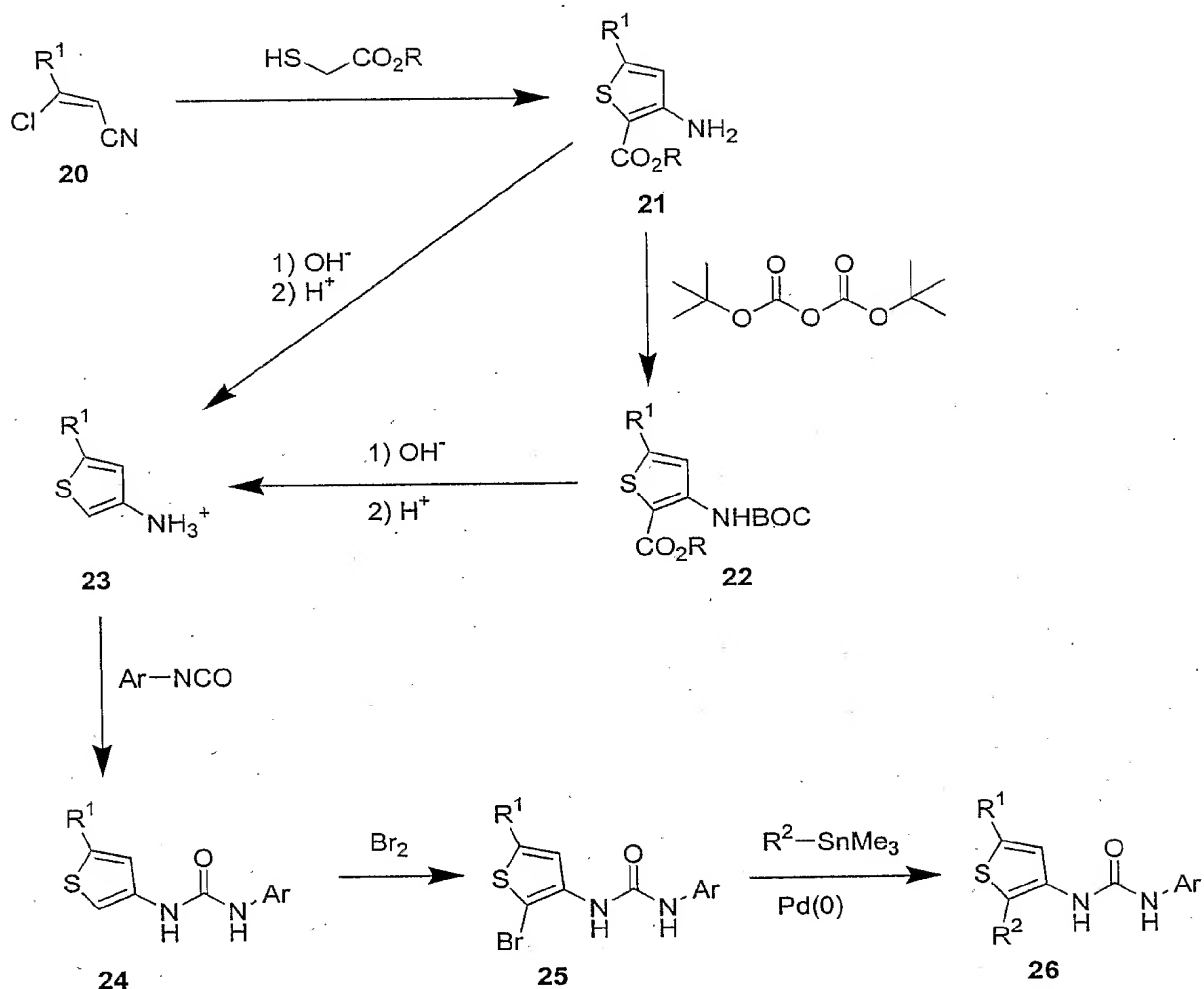
Scheme III Selected Nucleophilic Aromatic Substitution using Nitroaryls

As shown in Scheme IV, urea formation may involve reaction of a heteroaryl isocyanate (12) with an aryl amine (11). The heteroaryl isocyanate may be synthesized from a heteroaryl amine by treatment with phosgene or a phosgene equivalent, such as trichloromethyl chloroformate (diphosgene), bis(trichloromethyl) carbonate (triphosgene), or *N,N'*-carbonyldiimidazole (CDI). The isocyanate may also be derived from a heterocyclic carboxylic acid derivative, such as an ester, an acid halide or an anhydride by a Curtius-type rearrangement. Thus, reaction of acid derivative 16 with an azide source, followed by rearrangement affords the isocyanate. The corresponding carboxylic acid (17) may also be subjected to Curtius-type rearrangements using diphenylphosphoryl azide (DPPA) or a similar reagent. A urea may also be generated from the reaction of an aryl isocyanate (15) with a heterocyclic amine.



Scheme IV Selected Methods of Urea Formation (Het = heterocycle)

Finally, ureas may be further manipulated using methods familiar to those skilled in the art. For example, 2-aryl and 2-heteroarylthienyl ureas are available from the corresponding 2-halothienyl urea through transition metal mediated cross coupling reactions (exemplified with 2-bromothiophene **25**, Scheme V). Thus, reaction of nitrile **20** with an α -thioacetate ester gives 5-substituted-3-amino-2-thiophenecarboxylate **21** (Ishizaki et al. JP 6025221). Decarboxylation of ester **21** may be achieved by protection of the amine, for example as the *tert*-butoxy (BOC) carbamate (**22**), followed by saponification and treatment with acid. When BOC protection is used, decarboxylation may be accompanied by deprotection giving the substituted 3-thiopheneammonium salt **23**. Alternatively, ammonium salt **23** may be directly generated through saponification of ester **21** followed by treatment with acid. Following urea formation as described above, bromination affords penultimate halothiophene **25**. Palladium mediated cross coupling of thiophene **25** with an appropriate tributyl- or trimethyltin (R^2 = aryl or heteroaryl) then affords the desired 2-aryl- or 2-heteroarylthienyl urea.



Scheme V Synthesis and Interconversion of Ureas

5

Finally, ureas may be further manipulated using methods familiar to those skilled in the art.

10

The compounds may be administered orally, topically, parenterally, by inhalation or spray or vaginally, sublingually, or rectally in dosage unit formulations.

The term 'administration by injection' includes intravenous, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. Dermal administration may include topical application or transdermal administration. One or

more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.

5 Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable
10 for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc
15 and lubricants/surfactants such as sodium lauryl sulfate. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly
20 released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein
25 the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending
30 agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for

example, lecithin, or condensation products or an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and

esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

5

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

10

The compounds may also be administered in the form of suppositories for rectal or vaginal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal or vaginal temperature and will therefore melt in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

15

Compounds of the invention may also be administered transdermally using methods known to those skilled in the art (see, for example: Chien; "Transdermal Controlled Systemic Medications"; Marcel Dekker, Inc.; 1987. Lipp et al. WO94/04157 3Mar94). For example, a solution or suspension of a compound of Formula I in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with additional additives known to those skilled in the art, such as matrix materials and bacteriocides. After sterilization, the resulting mixture can be formulated following known procedures into dosage forms. In addition, on treatment with emulsifying agents and water, a solution or suspension of a compound of Formula I may be formulated into a lotion or salve.

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Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane,

chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include mixtures of one or more materials selected from lower alcohols, lower ketones, lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

5

Suitable penetration enhancing materials for transdermal delivery system are known to those skilled in the art, and include, for example, monohydroxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated C₈-C₁₈ fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated C₈-C₁₈ fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl isobutyl tertbutyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl maleate, or diisopropyl fumarate. Additional penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbide and diethyleneglycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures of one or more materials selected from monohydroxy or polyhydroxy alcohols, saturated or unsaturated C₈-C₁₈ fatty alcohols, saturated or unsaturated C₈-C₁₈ fatty acids, saturated or unsaturated fatty esters with up to 24 carbons, diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

25

Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers, styrenebutadiene copolymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix components. Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

30

For all regimens of use disclosed herein for compounds of Formula I, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regime will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily topical dosage regime will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily inhalation dosage regime will preferably be from 0.01 to 10 mg/Kg of total body weight. These dosages regimes can be achieved with multiple dosages within a single day or extended dosages, such as those given on a weekly or monthly basis.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be appreciated by one skilled in the art that the specific dose level for any given patient will depend upon a variety of factors, including, the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy.

It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of this invention given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of

administration, route of administration, and rate of excretion, drug combination and the severity of the condition undergoing therapy.

Specific preparations of the compounds of this invention are already
5 described in the patent literature, and can be adapted to the compounds of the present invention. For example, Miller S. et al, "Inhibition of p38 Kinase using Symmetrical and Unsymmetrical Diphenyl Ureas" *PCT Int. Appl.* WO 99 32463, Miller, S et al. "Inhibition of raf Kinase using Symmetrical and Unsymmetrical Substituted Diphenyl Ureas" *PCT Int. Appl.*, WO 99 32436, Dumas, J. et al., "Inhibition of p38 Kinase
10 Activity using Substituted Heterocyclic Ureas" *PCT Int. Appl.*, WO 99 32111, Dumas, J. et al., "Inhibition of RAF Kinase Activity using Substituted Heterocyclic Ureas" *PCT Int. Appl.*, WO 99 32106, Dumas, J. et al., "Method for the Treatment of Neoplasm by Inhibition of raf Kinase using N-Heteroaryl-N'-(hetero)arylureas" *PCT Int. Appl.*, WO 99 32106, Dumas, J. et al., "Inhibition of p38 Kinase Activity using
15 Aryl- and Heteroaryl- Substituted Heterocyclic Ureas" *PCT Int. Appl.*, WO 99 32110, Dumas, J., et al., "Inhibition of raf Kinase using Aryl- and Heteroaryl- Substituted Heterocyclic Ureas" *PCT Int. Appl.*, WO 99 32455, Riedl, B., et al., "O-Carboxy Aryl Substituted Diphenyl Ureas as raf Kinase Inhibitors" *PCT Int. Appl.*, WO 00 42012, Riedl, B., et al., "O-Carboxy Aryl Substituted Diphenyl Ureas as p38
20 Kinase Inhibitors" *PCT Int. Appl.*, WO 00 41698.

Methods for preparing the compounds of this invention are also described in the following U.S. applications, some of which correspond to the PCT applications listed above.

08/863,022, filed May 23, 1997;
25 08/996,344, filed December 22, 1997;
08/996,343, filed December 22, 1997;
08/996,181, filed December 22, 1997;
08/995,749, filed December 22, 1997;
08/995,750, filed December 22, 1997;
30 08/995,751, filed December 22, 1997;
09/083,399, filed May 22, 1998;
09/425,228, filed October 22, 1999;

09/777,920, filed February 7, 2001.

09/722,418 filed November 28, 2000

09/838,285, filed April 20, 2001;

09/838,286, filed April 20, 2001;

5 09/458,548, filed January 12, 2001;

09/948,915, filed September 10, 2001, and

Serial Number (attorney docket number: Bayer 34 V1), filed December 3, 2001.

10 The entire disclosure of all applications, patents and publications cited above and below are hereby incorporated by reference.

The compounds of this invention are producible from known compounds (or from starting materials which, in turn, are producible from known compounds), e.g., through the general preparative methods shown below. The activity of a given compound to inhibit angiogenesis activity can be routinely assayed, e.g., according to procedures disclosed below.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever. The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.

25

EXAMPLES

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon or dry nitrogen, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mmHg.

30

All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by weight.

Commercial grade reagents and solvents were used without further
5 purification.

Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 µm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure
10 to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, (d) immersion of the plate in a cerium sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.

15 Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Proton (¹H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me₄Si (δ 0.00) or residual protonated solvent (CHCl₃ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard.
20 Carbon (¹³C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDCl₃ δ 77.0; MeOD-d₃ δ 49.0; DMSO-d₆ δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) were
25 obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source was maintained at 250 °C. Electron impact ionization was performed with electron energy of 70 eV and a trap current of 300 µA. Liquid-caesium secondary ion mass spectra (FAB-MS), an updated version of fast atom bombardment were obtained
30 using a Kratos Concept 1-H spectrometer.

Chemical ionization mass spectra (CI-MS) were obtained using a Hewlett Packard MS-Engine (5989A) with methane as the reagent gas (1×10^{-4} torr to 2.5×10^{-4} torr). The direct insertion desorption chemical ionization (DCI) probe (Vaccumetrics, Inc.) was ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra were scanned from 50-800 amu at 2 sec per scan. HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C-18 column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-800 amu using a variable ion time according to the number of ions in the source.

Gas chromatography - ion selective mass spectra (GC-MS) were obtained with a Hewlett Packard 5890 gas chromatograph equipped with an HP-1 methyl silicone column (0.33 mM coating; 25 m x 0.2 mm) and a Hewlett Packard 5971 Mass Selective Detector (ionization energy 70 eV).

Elemental analyses were conducted by Robertson Microlit Labs, Madison NJ. All compounds displayed NMR spectra, LRMS and either elemental analysis or HRMS consistent with assigned structures.

List of Abbreviations and Acronyms:

AcOH	acetic acid
anh	anhydrous
BOC	<i>tert</i> -butoxycarbonyl
conc	concentrated
dec	decomposition
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EtOAc	ethyl acetate
EtOH	ethanol (100%)

Et ₂ O	diethyl ether
Et ₃ N	triethylamine
<i>m</i> -CPBA	3-chloroperoxybenzoic acid
MeOH	methanol
5 pet. ether	petroleum ether (boiling range 30-60 °C)
THF	tetrahydrofuran
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl

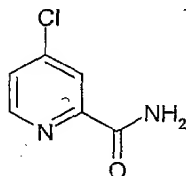
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EXAMPLE A

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-
yridyloxy)]phenyl} urea.

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Step 1: Preparation of 4-chloro-2-pyridinecarboxamide

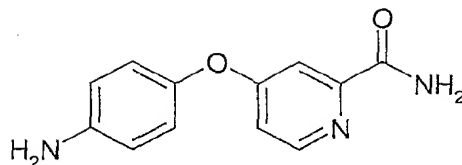


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To a stirred mixture of methyl 4-chloro-2-pyridinecarboxylate hydrochloride (1.0 g, 4.81 mmol) dissolved in conc. aqueous ammonia (32 mL) was added ammonium chloride (96.2 mg, 1.8 mmol, 0.37 equiv.), and the heterogeneous reaction mixture was stirred at ambient temperature for 16h. The reaction mixture was poured into EtOAc (500 mL) and water (300 mL). The organic layer was washed with water (2 x 300 mL) and a saturated NaCl solution (1 x 300 mL), dried (MgSO₄),
25 concentrated in *vacuo* to give 4-chloro-2-pyridinecarboxamide as a beige solid (604.3 mg, 80.3%); TLC (50% EtOAc / hexane) R_f 0.20; ¹H-NMR (DMSO-d₆) δ 8.61 (d, J = 5.4 Hz, 1H), 8.20 (broad s, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.81 (broad s, 1H), 7.76 to 7.73 (m, 1H).

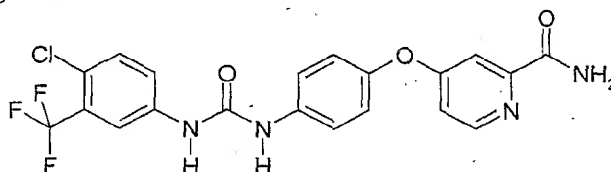
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Step 2: Preparation of 4-(4-aminophenoxy)-2-pyridinecarboxamide



To 4-aminophenol (418 mg, 3.83 mmol) in anhyd DMF (7.7 mL) was added potassium *tert*-butoxide (447 mg, 3.98 mmol, 1.04 equiv.) in one portion. The reaction mixture was stirred at room temperature for 2 h, and a solution of 4-chloro-2-pyridinecarboxamide (600 mg, 3.83 mmol, 1.0 equiv.) in anhyd DMF (4 mL) was then added. The reaction mixture was stirred at 80 °C for 3 days and poured into a mixture of EtOAc and a saturated NaCl solution. The organic layer was sequentially washed with a saturated NH₄Cl solution then a saturated NaCl solution, dried (MgSO₄), and concentrated under reduced pressure. The crude product was purified using MPLC chromatography (Biotage®; gradient from 100% EtOAc to followed by 10% MeOH / 50% EtOAc / 40% hexane) to give the 4-chloro-5-trifluoromethylaniline as a brown solid (510 mg, 58%). ¹H-NMR (DMSO-*d*₆) δ 8.43 (d, *J* = 5.7 Hz, 1H), 8.07 (br s, 1H), 7.66 (br s, 1H), 7.31 (d, *J* = 2.7 Hz, 1H), 7.07 (dd, *J* = 5.7 Hz, 2.7 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2 H), 6.62 (d, *J* = 8.7 Hz, 2H), 5.17 (broad s, 2H); HPLC EI-MS *m/z* 230 ((*M*+H)⁺).

Step 3: Preparation of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea

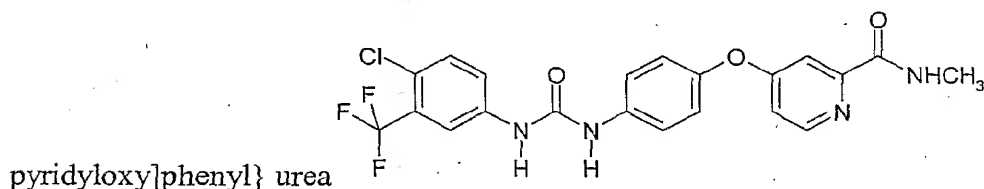


A mixture of 4-chloro-5-trifluoromethylaniline (451 mg, 2.31 mmol, 1.1 equiv.) and 1,1'-carbonyl diimidazole (419 mg, 2.54 mmol, 1.2 equiv.) in anhyd dichloroethane (5.5 mL) was stirred under argon at 65 °C for 16 h. Once cooled to room temperature, a solution of 4-(4-aminophenoxy)-2-pyridinecarboxamide (480 mg, 2.09 mmol) in anhyd THF (4.0 mL) was added, and the reaction mixture was stirred at 60°C for 4 h. The reaction mixture was poured into EtOAc, and the organic layer was washed with water (2x) and a saturated NaCl solution (1x), dried (MgSO₄), filtered, and evaporated in *vacuo*. Purification using MPLC chromatography (Biotage®; gradient from 100% EtOAc to 2% MeOH / EtOAc) gave N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea as a white solid (770 mg, 82%); TLC (EtOAc) *R_f* 0.11, 100% ethyl acetate ¹H-NMR (DMSO-*d*₆)

8 9.21 (s, 1H), 8.99 (s, 1H), 8.50 (d, $J = 5.6$ Hz, 1H), 8.11 (s, 1H), 8.10 (s, 1H), 7.69 (broad s, 1H), 7.64 (dd, $J = 8.2$ Hz, 2.1 Hz, 1H), 7.61 (s, 1H), 7.59 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 2.5$ Hz, 1H), 7.15 (d, $J = 8.9$ Hz, 2H), 7.14 (m, 1H); MS LC-MS ($MH^+ = 451$). Anal. calcd for $C_{20}H_{14}ClF_3N_4O_3$: C 53.29% H 3.13% N 12.43%. Found: C 53.33% H 3.21% N 12.60%;

Example B

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-N-methylcarbamoyl-4-



Step 1: 4-Chloro-*N*-methyl-2-pyridinecarboxamide is first synthesized from 4-chloropyridine-2-carbonyl chloride by adding 4-chloropyridine-2-carbonyl chloride HCl salt (7.0 g, 32.95 mmol) in portions to a mixture of a 2.0 M methylamine solution in THF (100 mL) and MeOH (20 mL) at 0 °C. The resulting mixture is stored at 3 °C for 4 h, then concentrated under reduced pressure. The resulting nearly dry solids are suspended in EtOAc (100 mL) and filtered. The filtrate is washed with a saturated NaCl solution (2 x 100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide 4-chloro-*N*-methyl-2-pyridinecarboxamide as a yellow, crystalline solid.

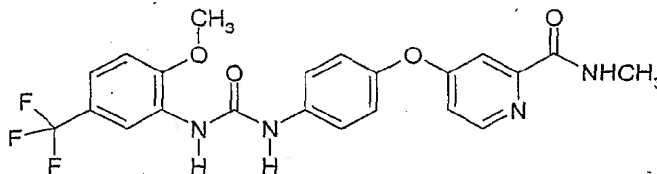
Step 2: A solution of 4-aminophenol (9.60 g, 88.0 mmol) in anh. DMF (150 mL) is treated with potassium *tert*-butoxide (10.29 g, 91.7 mmol), and the reddish-brown mixture is stirred at room temp. for 2 h. The contents are treated with 4-chloro-*N*-methyl-2-pyridinecarboxamide (15.0 g, 87.9 mmol) from Step 1 and K_2CO_3 (6.50 g, 47.0 mmol) and then heated at 80 °C for 8 h. The mixture is cooled to room temp. and separated between EtOAc (500 mL) and a saturated NaCl solution (500 mL). The aqueous phase is back-extracted with EtOAc (300 mL). The combined organic layers are washed with a saturated NaCl solution (4 x 1000 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting solids are dried under reduced

pressure at 35 °C for 3 h to afford 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline as a light-brown solid. ¹H-NMR (DMSO-*d*₆) δ 2.77 (d, *J*=4.8 Hz, 3H), 5.17 (br s, 2H), 6.64, 6.86 (AA'BB' quartet, *J*=8.4 Hz, 4H), 7.06 (dd, *J*=5.5, 2.5 Hz, 1H), 7.33 (d, *J*=2.5 Hz, 1H), 8.44 (d, *J*=5.5 Hz, 1H), 8.73 (br d, 1H); HPLC ES-MS *m/z* 244 ((*M*+H)⁺).

Step 3: A solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (14.60 g, 65.90 mmol) in CH₂Cl₂ (35 mL) is added dropwise to a suspension of 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline from Step 2; (16.0 g, 65.77 mmol) in CH₂Cl₂ (35 mL) at 0 °C. The resulting mixture is stirred at room temp. for 22 h. The resulting yellow solids are removed by filtration, then washed with CH₂Cl₂ (2 x 30 mL) and dried under reduced pressure (approximately 1 mmHg) to afford *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as an off-white solid: mp 207-209 °C; ¹H-NMR (DMSO-*d*₆) δ 2.77 (d, *J*=4.8 Hz, 3H), 7.16 (m, 3H), 7.37 (d, *J*=2.5 Hz, 1H), 7.62 (m, 4H), 8.11 (d, *J*=2.5 Hz, 1H), 8.49 (d, *J*=5.5 Hz, 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS *m/z* 465 ((*M*+H)⁺).

Example C

N-[2-methoxy-5-(trifluoromethyl)phenyl]-*N'*-(4-[2-*N*-methylcarbamoyl-4-pyridyloxy]phenyl) urea



Step 1: 4-Chloro-*N*-methyl-2-pyridinecarboxamide is first synthesized from 4-chloropyridine-2-carbonyl chloride by adding 4-chloropyridine-2-carbonyl chloride HCl salt (7.0 g, 32.95 mmol) in portions to a mixture of a 2.0 M methylamine solution in THF (100 mL) and MeOH (20 mL) at 0 °C. The resulting mixture is stored at 3 °C for 4 h, then concentrated under reduced pressure. The resulting nearly dry solids are

suspended in EtOAc (100 mL) and filtered. The filtrate is washed with a saturated NaCl solution (2 x 100 mL), dried (Na₂SO₄) and concentrated under reduced pressure to provide 4-chloro-*N*-methyl-2-pyridinecarboxamide as a yellow, crystalline solid.

5 Step 2: A solution of 4-aminophenol (9.60 g, 88.0 mmol) in anh. DMF (150 mL) is treated with potassium *tert*-butoxide (10.29 g, 91.7 mmol), and the reddish-brown mixture is stirred at room temp. for 2 h. The contents are treated with 4-chloro-*N*-methyl-2-pyridinecarboxamide (15.0 g, 87.9 mmol) from Step 1 and K₂CO₃ (6.50 g, 47.0 mmol) and then heated at 80 °C for 8 h. The mixture is cooled to room temp.
10 and separated between EtOAc (500 mL) and a saturated NaCl solution (500 mL). The aqueous phase is back-extracted with EtOAc (300 mL). The combined organic layers are washed with a saturated NaCl solution (4 x 1000 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The resulting solids are dried under reduced pressure at 35 °C for 3 h to afford 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline as a
15 light-brown solid. ¹H-NMR (DMSO-d₆) δ 2.77 (d, *J*=4.8 Hz, 3H), 5.17 (br s, 2H), 6.64, 6.86 (AA'BB' quartet, *J*=8.4 Hz, 4H), 7.06 (dd, *J*=5.5, 2.5 Hz, 1H), 7.33 (d, *J*=2.5 Hz, 1H), 8.44 (d, *J*=5.5 Hz, 1H), 8.73 (br d, 1H); HPLC ES-MS *m/z* 244 ((M+H)⁺).

20 Step 3: To a solution of 2-methoxy-5-(trifluoromethyl)aniline (0.15 g) in anh CH₂Cl₂ (15 mL) at 0 °C is added CDI (0.13 g). The resulting solution is allowed to warm to room temp. over 1 h, is stirred at room temp. for 16 h, then is treated with 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (0.18 g) from Step 2. The resulting yellow solution is stirred at room temp. for 72 h, then is treated with H₂O (125 mL). The
25 resulting aqueous mixture is extracted with EtOAc (2 x 150 mL). The combined organics are washed with a saturated NaCl solution (100 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue is triturated (90% EtOAc/10% hexane). The resulting white solids are collected by filtration and washed with EtOAc. The filtrate is concentrated under reduced pressure and the residual oil
30 purified by column chromatography (gradient from 33% EtOAc/67% hexane to 50% EtOAc/50% hexane to 100% EtOAc) to give *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as

a light tan solid: TLC (100% EtOAc) R_f 0.62; ^1H NMR ($\text{DMSO}-d_6$) δ 2.76 (d, $J=4.8$ Hz, 3H), 3.96 (s, 3H), 7.1-7.6 and 8.4-8.6 (m, 11H), 8.75 (d, $J=4.8$ Hz, 1H), 9.55 (s, 1 H); FAB-MS m/z 461 ($(\text{M}+\text{H})^+$).

5

BIOLOGICAL EXAMPLES

KDR (VEGFR2) Assay:

The cytosolic kinase domain of KDR kinase was expressed as a 6His fusion protein in Sf9 insect cells. The KDR kinase domain fusion protein was purified over a
10 Ni $^{++}$ chelating column. Ninety-six well ELISA plates were coated with 5 μl HEPES buffer (20 mM poly(Glu4;Tyr1) (Sigma Chemical Co., St. Louis, MO) in 100 μk HEPES buffer (20 mM HEPES, pH 7.5, 150 mM Na Cl, 0.02% Thimerosal) at 4° overnight. Before use, the plate was washed with HEPES, NaCl buffer and the plates were blocked with 1% BSA, 0.1% Tween 20 in HEPES, NaCl buffer.

15

Test compounds were serially diluted in 100% DMSO from 4 mM to 0.12 μM in half-log dilutions. These dilutions were further diluted twenty fold in H_2O to obtain compound solutions in 5% DMSO. Following loading of the assay plate with 85 μl of assay buffer (20 mM HEPES, pH 7.5, 100 mM KCl, 10 mM MgCl_2 , 3 mM MnCl_2 , 0.05% glycerol, 0.005% Triton X-100, 1 mM γ -mercaptoethanol, with or
20 without 3.3 μM ATP), 5 μl of the diluted compounds were added to a final assay volume of 100 μl . Final concentrations were between 10 μM , and 0.3 mM in 0.25% DMSO. The assay was initiated by the addition of 10 μl (30 ng) of KDR kinase domain.

20

25

The assay was incubated with test compound or vehicle alone with gentle agitation at room temperature for 60 minutes. The wells were washed and phosphotyrosines (PY) were probed with an anti-phosphotyrosine (PY), mAb clone 4G10 (Upstate Biotechnology, Lake Placid, NY). PY/anti-PY complexes were detected with an anti-mouse IgG/HRP conjugate (Amersham International plc,
30 Buckinghamshire, England). Phosphotyrosine was quantitated by incubating with 100 μl 3, 3', 5, 5' tetramethylbenzidine solution (Kirkegaard and Perry, TMB Microwell 1 Component peroxidase substrate). Color development was arrested by the addition of

30

100 µl 1% HCl-based stop solution (Kirkegaard and Perry, TMB 1 Component Stop Solution).

Optical densities were determined spectrophotometrically at 450 nm in a 96-well plate reader, SpectraMax 250 (Molecular Devices). Background (no ATP in assay) OD values were subtracted from all Ods and the percent inhibition was calculated according to the equation:

$$\% \text{ Inhibition} = \frac{\text{OD}(\text{vehicle control}) - \text{OD}(\text{with compound}) \times 100}{\text{OD}(\text{vehicle control}) - \text{OD}(\text{no ATP added})}$$

The IC₅₀ values were determined with a least squares analysis program using compound concentration versus percent inhibition.

The following compounds were tested in the assay described above and were found to have either an IC₅₀ of less than 10 micromolar or showed greater than 30% inhibition at 1 micromolar. Compound names were generated using NomenclatorTM v 3.0 and may differ from those in the patent applications.

From WO 1999/32463:

Entry No	Name
73	N-[5-(tert-butyl)-2-(3-thienyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
96	{[4-(4-methoxyphenoxy)phenyl]amino}-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
99	N-[2-methoxy-5-(trifluoromethyl)phenyl][(3-(4-pyridylthio)phenyl)amino]carboxamide
100	N-[2-methoxy-5-(trifluoromethyl)phenyl][(3-(4-pyridylthio)phenyl)amino]carboxamide
101	N-[2-methoxy-5-(trifluoromethyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide

From WO 1999/32436:

Entry No	Name
11	N-[5-(tert-butyl)-2-methoxyphenyl][(3-(4-pyridylthio)phenyl)amino]carboxamide
12	N-[5-(tert-butyl)-2-(3-thienyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
17	N-[3-(tert-butyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
23	{[3-(tert-butyl)phenyl]amino}-N-(4-(3-pyridyl)phenyl)carboxamide
33	{[4-(4-methoxyphenoxy)phenyl]amino}-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
36	N-[2-methoxy-5-(trifluoromethyl)phenyl][(3-(4-pyridylthio)phenyl)amino]carboxamide
37	N-[2-methoxy-5-(trifluoromethyl)phenyl][(3-(4-pyridylthio)phenyl)amino]carboxamide
38	N-[2-methoxy-5-(trifluoromethyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
56	N-[2-methoxy-5-(trifluoromethyl)phenyl]{[3-(2-methyl(4-pyridyloxy))phenyl]amino}carboxamide
70	[(3-chloro-4-(6-quinolyloxy)phenyl)amino]-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
81	[(4-(4-pyridyloxy)phenyl)amino]-N-[3-(trifluoromethyl)phenyl]carboxamide
82	N-[2-chloro-5-(trifluoromethyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
83	N-[2-fluoro-5-(trifluoromethyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
91	{[4-chloro-3-(trifluoromethyl)phenyl]amino}-N-(2-methyl-4-(3-pyridyloxy)phenyl)carboxamide
102	N-[4-chloro-3-(trifluoromethyl)phenyl][(4-(4-

	pyridyloxy)phenyl)amino]carboxamide
103	N-[4-chloro-3-(trifluoromethyl)phenyl][4-(4-methoxyphenoxy)phenyl]amino} carboxamide
105	{[4-chloro-3-(trifluoromethyl)phenyl]amino}-N-[3-(4-pyridylcarbonyl)phenyl]carboxamide
106	{[4-chloro-3-(trifluoromethyl)phenyl]amino}-N-[3-(2-methyl(4-pyridyloxy))phenyl]carboxamide
119	N-[4-fluoro-3-(trifluoromethyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
132	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
133	N-[5-methoxy-3-(trifluoromethyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
135	[(3-bromo-4-chlorophenyl)amino]-N-(4-(4-pyridyloxy)phenyl)carboxamide
136	[(4-(4-pyridyloxy)phenyl)amino]-N-[3-(trifluoromethoxy)phenyl]carboxamide
141	N-[3,5-bis(trifluoromethyl)phenyl][(4-(4-pyridyloxy)phenyl)amino]carboxamide

From WO 1999/32111:

Entry No	Name
18	N-[5-(tert-butyl)isoxazol-3-yl][(4-(4-pyridylthio)phenyl)amino]carboxamide
32	{[5-(tert-butyl)isoxazol-3-yl]amino}-N-(3-(4-pyridylthio)phenyl)carboxamide
53	N-[5-(tert-butyl)isoxazol-3-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
59	N-[5-(tert-butyl)isoxazol-3-yl][(4-(3-pyridyloxy)phenyl)amino]carboxamide

67	{3-[4-({[5-(tert-butyl)isoxazol-3-yl]amino}carbonylamino)phenoxy]phenyl}-N-methylcarboxamide
85	{[5-(tert-butyl)isoxazol-3-yl]amino}-N-[3-(2-methyl(4-pyridyloxy))phenyl]carboxamide
86	N-[5-(tert-butyl)isoxazol-3-yl]{[4-(2-methyl(4-pyridyloxy))phenyl]amino}carboxamide
103	4-[4-({[5-(tert-butyl)isoxazol-3-yl]amino}carbonylamino)phenoxy]pyridine-2-carboxamide
104	{[5-(tert-butyl)isoxazol-3-yl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl}carboxamide
105	4-[3-({N-[5-(tert-butyl)isoxazol-3-yl]carbamoyl}amino)phenoxy]pyridine-2-carboxamide
106	3-[4-({[5-(tert-butyl)isoxazol-3-yl]amino}carbonylamino)phenoxy]benzamide
143	N-[3-(methylethyl)isoxazol-5-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
146	N-(3-cyclobutylisoxazol-5-yl)[(4-(4-pyridyloxy)phenyl)amino]carboxamide
147	N-(3-cyclobutylisoxazol-5-yl)[(4-(6-quinolyloxy)phenyl)amino]carboxamide
162	{[3-(tert-butyl)isoxazol-5-yl]amino}-N-(3-(4-pyridylthio)phenyl)carboxamide
163	N-[3-(tert-butyl)isoxazol-5-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
164	N-[3-(tert-butyl)isoxazol-5-yl]{[4-(4-methoxyphenoxy)phenyl]amino}carboxamide
188	N-[3-(1,1-dimethylpropyl)isoxazol-5-yl][(3-(4-pyridylthio)phenyl)amino]carboxamide
195	N-[3-(1,1-dimethylpropyl)isoxazol-5-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide

220	{[3-(tert-butyl)pyrazol-5-yl]amino}-N-(3-(4-pyridylthio)phenyl)carboxamide
221	N-[3-(tert-butyl)pyrazol-5-yl][(4-(4-pyridylthio)phenyl)amino]carboxamide
222	{3-[4-({[3-(tert-butyl)pyrazol-5-yl]amino}carbonylamino)phenoxy]phenyl}-N-methylcarboxamide, 2,2,2-trifluoroacetic acid
225	N-[3-(tert-butyl)-1-methylpyrazol-5-yl][(3-(4-pyridylthio)phenyl)amino]carboxamide
251	N-[3-(tert-butyl)-1-methylpyrazol-5-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
261	N-[3-(tert-butyl)-1-methylpyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
266	N-[3-(tert-butyl)-1-methylpyrazol-5-yl]{[4-(4-pyridylmethoxy)phenyl]amino}carboxamide
277	tert-butyl 3-(tert-butyl)-5-[(4-[3-(N-methylcarbamoyl)phenoxy]phenyl)amino]carbonylamino]pyrazolecarboxylate
280	N-[5-(tert-butyl)(1,3,4-thiadiazol-2-yl)][(4-(4-pyridyloxy)phenyl)amino]carboxamide
281	{[5-(tert-butyl)(1,3,4-thiadiazol-2-yl)]amino}-N-(3-(4-pyridylthio)phenyl)carboxamide
284	N-[5-(tert-butyl)(3-thienyl)][(4-(3-pyridyloxy)phenyl)amino]carboxamide
293	N-[5-(tert-butyl)(3-thienyl)][(4-(4-pyridyloxy)phenyl)amino]carboxamide
299	N-(6-chloro(1H-indazol-3-yl))[(4-(4-pyridyloxy)phenyl)amino]carboxamide
302	((4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl)amino)-N-(1-methyl-3-phenylpyrazol-5-yl)carboxamide

From WO 1999/

Entry No	Name
21	N-[5-(tert-butyl)isoxazol-3-yl][(4-(4-pyridylthio)phenyl)amino]carboxamide
42	{[5-(tert-butyl)isoxazol-3-yl]amino}-N-(3-(4-pyridylthio)phenyl)carboxamide
59	N-[5-(tert-butyl)isoxazol-3-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
64	N-[5-(tert-butyl)isoxazol-3-yl][(4-(3-pyridyloxy)phenyl)amino]carboxamide
69	{3-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)phenoxy]phenyl}-N-methylcarboxamide
81	{[5-(tert-butyl)isoxazol-3-yl]amino}-N-[3-(2-methyl(4-pyridyloxy))phenyl]carboxamide
82	N-[5-(tert-butyl)isoxazol-3-yl]{[4-(2-methyl(4-pyridyloxy))phenyl]amino}carboxamide
101	{4-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide
103	4-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)phenoxy]pyridine-2-carboxamide
104	4-[3-({N-[5-(tert-butyl)isoxazol-3-yl]carbonyl}amino)phenoxy]pyridine-2-carboxamide
105	{[5-(tert-butyl)isoxazol-3-yl]amino}-N-{3-[2-(N-methylcarbonyl)(4-pyridyloxy)]phenyl}carboxamide
106	3-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)phenoxy]benzamide
118	{4-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)-3-chlorophenoxy](2-pyridyl)}-N-methylcarboxamide

124	{3-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)phenoxy]phenyl}-N-(2-morpholin-4-ylethyl)carboxamide
125	{4-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)phenoxy](2-pyridyl)}-N-ethylcarboxamide
126	{4-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)-2-chlorophenoxy](2-pyridyl)}-N-methylcarboxamide
127	{[5-(tert-butyl)isoxazol-3-yl]amino}-N-{2-methyl-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl}carboxamide
128	{[5-(tert-butyl)isoxazol-3-yl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl}carboxamide
130	{3-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)phenoxy]phenyl}-N-(3-pyridyl)carboxamide
140	{4-[4-({[5-(tert-butyl)isoxazol-3-yl]amino} carbonylamino)phenylthio](2-pyridyl)}-N-methylcarboxamide
182	N-methyl{4-[4-({[3-(methylethyl)isoxazol-5-yl]amino} carbonylamino)phenoxy](2-pyridyl)}carboxamide
186	N-methyl{4-[3-({[3-(methylethyl)isoxazol-5-yl]amino} carbonylamino)phenoxy](2-pyridyl)}carboxamide
187	N-(3-cyclobutylisoxazol-5-yl)[(4-(6-quinolyloxy)phenyl)amino]carboxamide
188	N-(3-cyclobutylisoxazol-5-yl)[(4-(4-pyridyloxy)phenyl)amino]carboxamide
194	N-[3-(tert-butyl)isoxazol-5-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
195	N-[3-(tert-butyl)isoxazol-5-yl]{[4-(4-methoxyphenoxy)phenyl]amino}carboxamide
206	{[3-(tert-butyl)isoxazol-5-yl]amino}-N-(3-(4-

	pyridylthio)phenyl)carboxamide
212	N-[3-(tert-butyl)isoxazol-5-yl]{[4-(1,3-dioxoisindolin-5-yloxy)phenyl]amino}carboxamide
213	{[3-(tert-butyl)isoxazol-5-yl]amino}-N-[4-(1-oxoisindolin-5-yloxy)phenyl]carboxamide
214	{4-[4-({[3-(tert-butyl)isoxazol-5-yl]amino}carbonylamino)phenoxy](2-pyridyl)}-N-ethylcarboxamide
215	{4-[4-({[3-(tert-butyl)isoxazol-5-yl]amino}carbonylamino)-2-chlorophenoxy](2-pyridyl)}-N-methylcarboxamide
216	{[3-(tert-butyl)isoxazol-5-yl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl}carboxamide
217	{4-[4-({[3-(tert-butyl)isoxazol-5-yl]amino}carbonylamino)phenylthio](2-pyridyl)}-N-methylcarboxamide
218	{4-[4-({[3-(tert-butyl)isoxazol-5-yl]amino}carbonylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide
228	{[3-(tert-butyl)isoxazol-5-yl]amino}-N-[3-(6-methyl(3-pyridyloxy))phenyl]carboxamide
240	N-[3-(tert-butyl)isoxazol-5-yl][(6-(4-pyridylthio)(3-pyridyl))amino]carboxamide
247	{[3-(tert-butyl)isoxazol-5-yl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl}carboxamide
253	N-[3-(1,1-dimethylpropyl)isoxazol-5-yl][(3-(4-pyridylthio)phenyl)amino]carboxamide
255	N-[3-(1,1-dimethylpropyl)isoxazol-5-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
261	N-[3-(1,1-dimethylpropyl)isoxazol-5-yl]({4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl}amino)carboxamide
263	N-[3-(1,1-dimethylpropyl)isoxazol-5-yl]{[4-(2-methyl(4-

	pyridylthio))phenyl]amino} carboxamide
292	N-[3-(tert-butyl)pyrazol-5-yl] {[4-(6-methyl(3-pyridyloxy))phenyl]amino} carboxamide
298	{[3-(tert-butyl)pyrazol-5-yl]amino}-N-(3-(4-pyridylthio)phenyl)carboxamide
299	N-[3-(tert-butyl)pyrazol-5-yl] [(4-(4-pyridylthio)phenyl)amino] carboxamide
300	{3-[4-({[3-(tert-butyl)pyrazol-5-yl]amino} carbonylamino)phenoxy]phenyl}-N-methylcarboxamide, 2,2,2-trifluoroacetic acid
304	N-[3-(tert-butyl)-1-methylpyrazol-5-yl] {[4-(4-pyridylmethoxy)phenyl]amino} carboxamide
305	{5-[4-({[3-(tert-butyl)-1-methylpyrazol-5-yl]amino} carbonylamino)phenoxy]-2-methoxyphenyl}-N-methylcarboxamide
309	N-[3-(tert-butyl)-1-methylpyrazol-5-yl] [(3-(4-pyridylthio)phenyl)amino] carboxamide
321	N-[3-(tert-butyl)-1-methylpyrazol-5-yl] [(4-(4-pyridyloxy)phenyl)amino] carboxamide
326	N-[3-(tert-butyl)-1-methylpyrazol-5-yl] {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
339	tert-butyl 3-(tert-butyl)-5-[(4-[3-(N-methylcarbamoyl)phenoxy]phenyl)amino] carbonylamino] pyrazolecarboxylate
341	N-[5-(tert-butyl)(1,3,4-thiadiazol-2-yl)] [(4-(4-pyridyloxy)phenyl)amino] carboxamide
342	{[5-(tert-butyl)(1,3,4-thiadiazol-2-yl)]amino}-N-(3-(4-pyridylthio)phenyl)carboxamide
356	N-[5-(tert-butyl)(1,3,4-thiadiazol-2-yl)] {[6-(6-methyl(3-pyridyloxy))(3-pyridyl)]amino} carboxamide
366	N-[5-(1,1-dimethylpropyl)(1,3,4-thiadiazol-2-yl)] [(4-(4-

	pyridyloxy)phenyl)amino]carboxamide
367	N-[5-(1,1-dimethylpropyl)(1,3,4-thiadiazol-2-yl)][(3-(4-pyridylthio)phenyl)amino]carboxamide
376	N-[5-(tert-butyl)(3-thienyl)][(4-(3-pyridyloxy)phenyl)amino]carboxamide
388	{3-[4-({[5-(tert-butyl)(1,3,4-oxadiazol-2-yl)]amino}carbonylamino)phenoxy]phenyl}-N-ethylcarboxamide
389	{3-[4-({[5-(tert-butyl)(1,3,4-oxadiazol-2-yl)]amino}carbonylamino)phenoxy]phenyl}-N-(methylethyl)carboxamide
390	{3-[4-({[5-(tert-butyl)(1,3,4-oxadiazol-2-yl)]amino}carbonylamino)phenoxy]phenyl}-N-methylcarboxamide
391	N-[5-(tert-butyl)(1,3,4-oxadiazol-2-yl)][(4-(4-pyridyloxy)phenyl)amino]carboxamide
392	N-(3-cyclopropyl-1-methylpyrazol-5-yl)[(4-(6-quinolyloxy)phenyl)amino]carboxamide
393	({4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl}amino)-N-(1-methyl-3-phenylpyrazol-5-yl)carboxamide
395	N-[2-(tert-butyl)(1,3-thiazol-5-yl)][{4-(6-methyl(3-pyridyloxy))phenyl]amino}carboxamide

From WO 1999/32110

Entry No	Name
1	[(2,3-dichlorophenyl)amino]-N-[3-(tert-butyl)-1-phenylpyrazol-5-yl]carboxamide
2	N-[1-(4-aminophenyl)-3-(tert-butyl)pyrazol-5-yl][(2,3-dichlorophenyl)amino]carboxamide
11	N-[1-(3-aminophenyl)-3-(tert-butyl)pyrazol-5-yl][(2,3-

	dichlorophenyl)amino]carboxamide
18	N-[3-(3-(tert-butyl)-5- {[4-(4-phenoxyphenyl) amino]carbonylamino} pyrazolyl)phenyl]acetamide
23	N-[1-(2,6-dichlorophenyl)-3-(tert-butyl)pyrazol-5-yl] {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
24	N-[3-(tert-butyl)-1-(4-fluorophenyl)pyrazol-5-yl] {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
25	N-[3-(tert-butyl)-1-(2-methylphenyl)pyrazol-5-yl] {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
26	N-[3-(tert-butyl)-1-(3-fluorophenyl)pyrazol-5-yl] {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
27	N-{3-(tert-butyl)-1-[4-(methylsulfonyl)phenyl]pyrazol-5-yl} {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
28	N-[3-(tert-butyl)-1-(4-nitrophenyl)pyrazol-5-yl] {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
29	N-[3-(tert-butyl)-1-(3-methoxyphenyl)pyrazol-5-yl] {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
30	N-[1-(3-aminophenyl)-3-(tert-butyl)pyrazol-5-yl] {[4-(4-pyridylmethyl)phenyl]amino} carboxamide
32	N-[1-(3-aminophenyl)-3-(tert-butyl)pyrazol-5-yl][(4-(4-pyridylthio)phenyl)amino]carboxamide
34	N-[3-(tert-butyl)-1-(3-fluorophenyl)pyrazol-5-yl][(3-(4-pyridylthio)phenyl)amino]carboxamide
35	N-[3-(tert-butyl)-1-(4-fluorophenyl)pyrazol-5-yl][(3-(4-pyridylthio)phenyl)amino]carboxamide
36	N-[3-(tert-butyl)-1-(3-fluorophenyl)pyrazol-5-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide
37	N-[3-(tert-butyl)-1-(4-fluorophenyl)pyrazol-5-yl][(4-(4-pyridyloxy)phenyl)amino]carboxamide

From WO 1999/32455

Entry No	Name
1	[(2,3-dichlorophenyl)amino]-N-[3-(tert-butyl)-1-phenylpyrazol-5-yl]carboxamide
2	N-[1-(4-aminophenyl)-3-(tert-butyl)pyrazol-5-yl][(2,3-dichlorophenyl)amino]carboxamide
14	N-[1-(3-aminophenyl)-3-(tert-butyl)pyrazol-5-yl][(2,3-dichlorophenyl)amino]carboxamide
22	N-[3-(3-(tert-butyl)-5-{{(4-phenoxyphenyl)amino}carbonylamino}pyrazolyl)phenyl]acetamide
27	N-[1-(2,6-dichlorophenyl)-3-(tert-butyl)pyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
28	N-[3-(tert-butyl)-1-(4-fluorophenyl)pyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
29	N-[3-(tert-butyl)-1-(2-methylphenyl)pyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
30	N-[3-(tert-butyl)-1-(3-fluorophenyl)pyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
31	N-[3-(tert-butyl)-1-[4-(methylsulfonyl)phenyl]pyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
32	N-[3-(tert-butyl)-1-(4-nitrophenyl)pyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
33	N-[3-(tert-butyl)-1-(3-methoxyphenyl)pyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
34	N-[1-(3-aminophenyl)-3-(tert-butyl)pyrazol-5-yl]{[4-(4-pyridylmethyl)phenyl]amino}carboxamide
36	N-[1-(3-aminophenyl)-3-(tert-butyl)pyrazol-5-yl][(4-(4-pyridylthio)phenyl)amino]carboxamide

From WO 2000/41698

Entry No	Name
1	{3-[4-({3-(tert-butyl)phenyl]amino} carbonylamino)phenoxy]phenyl}-N-methylcarboxamide
11	N-[2-methoxy-5-(trifluoromethyl)phenyl]({3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
12	4-[3-({N-[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl} amino)phenoxy]pyridine-2-carboxamide
13	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
14	4-[4-({N-[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl} amino)phenoxy]pyridine-2-carboxamide
16	{4-[4-({N-[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl} amino)-3-methylphenoxy](2-pyridyl)}-N-methylcarboxamide
17	((2-chloro-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
19	((4-[2-(N-ethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
20	((3-chloro-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
22	3-[4-({N-[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl} amino)phenoxy]benzamide
24	((4-[2-(N,N-dimethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
27	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl} amino)carboxamide
29	N-[2-methoxy-5-(trifluoromethyl)phenyl]({3-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl} amino)carboxamide
31	N-[2-methoxy-5-(trifluoromethyl)phenyl][(4-{5-[N-(2-morpholin-4-ylethyl)carbamoyl](3-pyridyloxy)}phenyl)amino]carboxamide
32	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[5-(N-

	methylcarbamoyl)(3-pyridyloxy)]phenyl} amino)carboxamide
34	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[3-(N-(3-pyridyl)carbamoyl)phenoxy]phenyl} amino)carboxamide
42	{4-[4-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide
43	4-[4-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenoxy]pyridine-2-carboxamide
44	4-[3-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenoxy]pyridine-2-carboxamide
45	{[4-chloro-3-(trifluoromethyl)phenyl] amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} carboxamide
47	{[4-chloro-3-(trifluoromethyl)phenyl] amino}-N-{2-methyl-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} carboxamide
49	{4-[3-chloro-4-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide
51	N-[4-chloro-3-(trifluoromethyl)phenyl]({4-[2-(N-ethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
61	{3-[4-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenoxy]phenyl}-N-(2-morpholin-4-ylethyl)carboxamide
62	{3-[4-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenoxy]phenyl}-N-(2-piperidylethyl)carboxamide
65	{4-[4-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenylthio](2-pyridyl)}-N-methylcarboxamide
69	{[4-chloro-3-(trifluoromethyl)phenyl] amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl} carboxamide
70	{4-[4-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenoxy](2-pyridyl)}-N-(2-morpholin-4-ylethyl)carboxamide
72	{5-[4-({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonylamino)phenoxy](3-

	pyridyl}}-N-methylcarboxamide
75	N-[4-chloro-3-(trifluoromethyl)phenyl]({4-[3-(N-(3-pyridyl)carbamoyl)phenoxy]phenyl} amino)carboxamide
84	{4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy](2-pyridyl}}-N-(2-hydroxyethyl)carboxamide
87	{4-[4-({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonylamino)-2-chlorophenoxy](2-pyridyl}}-N-methylcarboxamide
88	N-[4-bromo-3-(trifluoromethyl)phenyl]({4-[2-(N-ethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
89	{[4-bromo-3-(trifluoromethyl)phenyl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} carboxamide
90	{[4-bromo-3-(trifluoromethyl)phenyl]amino}-N-{4-methyl-3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} carboxamide
93	{[4-bromo-3-(trifluoromethyl)phenyl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl} carboxamide
94	{4-[4-({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy](2-pyridyl}}-N-(2-morpholin-4-ylethyl)carboxamide
95	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
96	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({2-chloro-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
97	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({3-chloro-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
98	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
99	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({4-[2-(N-ethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide

From WO 2000/42012

Entry No	Name
1.	{3-[4-({[3-(tert-

	butyl)phenyl]amino} carbonylamino)phenoxy]phenyl}-N-methylcarboxamide
11	N-[2-methoxy-5-(trifluoromethyl)phenyl]({3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
12	4-[3-({N-[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl} amino)phenoxy]pyridine-2-carboxamide
13	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
14	4-[4-({N-[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl} amino)phenoxy]pyridine-2-carboxamide
16	{4-[4-({N-[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl} amino)-3-methylphenoxy](2-pyridyl)}-N-methylcarboxamide
17	({2-chloro-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
19	({4-[2-(N-ethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
20	({3-chloro-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
22	3-[4-({N-[2-methoxy-5-(trifluoromethyl)phenyl]carbamoyl} amino)phenoxy]benzamide
24	({4-[2-(N,N-dimethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)-N-[2-methoxy-5-(trifluoromethyl)phenyl]carboxamide
27	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl} amino)carboxamide
29	N-[2-methoxy-5-(trifluoromethyl)phenyl]({3-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl} amino)carboxamide
31	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[5-[N-(2-morpholin-4-ylethyl)carbamoyl](3-pyridyloxy)]phenyl} amino)carboxamide
32	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[5-(N-methylcarbamoyl)(3-pyridyloxy)]phenyl} amino)carboxamide
34	N-[2-methoxy-5-(trifluoromethyl)phenyl]({4-[3-(N-(3-

	pyridyl)carbamoyl)phenoxy]phenyl} amino)carboxamide
42	{4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide
43	4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy]pyridine-2-carboxamide
44	4-[3-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy]pyridine-2-carboxamide
45	{[4-chloro-3-(trifluoromethyl)phenyl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} carboxamide
47	{[4-chloro-3-(trifluoromethyl)phenyl]amino}-N-{2-methyl-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} carboxamide
49	{4-[3-chloro-4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy](2-pyridyl)}-N-methylcarboxamide
51	N-[4-chloro-3-(trifluoromethyl)phenyl]({4-[2-(N-ethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
61	{3-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy]phenyl}-N-(2-morpholin-4-ylethyl)carboxamide
62	{3-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy]phenyl}-N-(2-piperidylethyl)carboxamide
65	{4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenylthio](2-pyridyl)}-N-methylcarboxamide
69	{[4-chloro-3-(trifluoromethyl)phenyl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl} carboxamide
70	{4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy](2-pyridyl)}-N-(2-morpholin-4-ylethyl)carboxamide
72	{5-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy](3-pyridyl)}-N-methylcarboxamide
75	N-[4-chloro-3-(trifluoromethyl)phenyl]({4-[3-(N-(3-

	pyridyl)carbamoyl)phenoxy]phenyl} amino)carboxamide
84	{4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy](2-pyridyl)}-N-(2-hydroxyethyl)carboxamide
87	{4-[4-({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonylamino)-2-chlorophenoxy](2-pyridyl)}-N-methylcarboxamide
88	N-[4-bromo-3-(trifluoromethyl)phenyl]({4-[2-(N-ethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
89	{[4-bromo-3-(trifluoromethyl)phenyl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} carboxamide
90	{[4-bromo-3-(trifluoromethyl)phenyl]amino}-N-{4-methyl-3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} carboxamide
93	{[4-bromo-3-(trifluoromethyl)phenyl]amino}-N-{3-[2-(N-methylcarbamoyl)(4-pyridylthio)]phenyl} carboxamide
94	{4-[4-({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonylamino)phenoxy](2-pyridyl)}-N-(2-morpholin-4-ylethyl)carboxamide
95	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
96	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({2-chloro-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
97	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({3-chloro-4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
98	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({3-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide
99	N-[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]({4-[2-(N-ethylcarbamoyl)(4-pyridyloxy)]phenyl} amino)carboxamide

From WO 2002/85859

Entry No	Name
16	[(4-fluorophenyl)amino]-N-(3-isoquinolyl)carboxamide
25	N-(2-methoxy(3-quinolyl))[(4-(4-

	pyridyloxy)phenyl)amino]carboxamide
27	N-(2-methoxy(3-quinolyl))[(3-(4-pyridylthio)phenyl)amino]carboxamide
28	N-[1-(4-methylpiperazinyl)(3-isoquinolyl)][(4-(4-pyridyloxy)phenyl)amino]carboxamide

From WO 2002/85857

Entry No	Name
25	N-(2-methoxy(3-quinolyl))[(4-(4-pyridyloxy)phenyl)amino]carboxamide
27	N-(2-methoxy(3-quinolyl))[(3-(4-pyridylthio)phenyl)amino]carboxamide
28	N-[1-(4-methylpiperazinyl)(3-isoquinolyl)][(4-(4-pyridyloxy)phenyl)amino]carboxamide

5 Cell mechanistic assay-Inhibition of 3T3 KDR phosphorylation:

NIH3T3 cells expressing the full length KDR receptor are grown in DMEM (Life Technologies, Inc., Grand Island, NY) supplemented with 10% newborn calf serum, low glucose, 25 mM/L sodium pyruvate, pyridoxine hydrochloride and 0.2 mg/ml of G418 (Life Technologies Inc., Grand Island, NY). The cells are maintained
 10 in collagen I-coated T75 flasks (Becton Dickinson Labware, Bedford, MA) in a humidified 5% CO₂ atmosphere at 37°C.

Fifteen thousand cells are plated into each well of a collagen I-coated 96-well plate in the DMEM growth medium. Six hours later, the cells are washed and the
 15 medium is replaced with DMEM without serum. After overnight culture to quiesce the cells, the medium is replaced by Dulbecco's phosphate-buffered saline (Life Technologies Inc., Grand Island, NY) with 0.1% bovine albumin (Sigma Chemical Co., St. Louis, MO). After adding various concentrations (0-300 nM) of test compounds to the cells in 1% final concentration of DMSO, the cells are incubated at
 20 room temperature for 30 minutes. Following VEGF stimulation, the buffer is

removed and the cells are lysed by addition of 150 µl of extraction buffer (50 mM Tris, pH 7.8, supplemented with 10% glycerol, 50 mM BGP, 2 mM EDTA, 10 mM NaF, 0.5 mM NaVO₄, and 0.3% TX-100) at 4°C for 30 minutes.

5 To assess receptor phosphorylation, 100 microliters of each cell lysate are added to the wells of an ELISA plate precoated with 300 ng of antibody C20 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA). Following a 60-minute incubation, the plate is washed and bound KDR is probed for phosphotyrosine using an anti-phosphotyrosine mAb clone 4G10 (Upstate Biotechnology, Lake Placid, NY). The
10 plate is washed and wells are incubated with anti-mouse IgG/HRP conjugate (Amersham International plc, Buckinghamshire, England) for 60 minutes. Wells are washed and phosphotyrosine is quantitated by addition of 100 µl per well of 3,3',5,5' tetramethylbenzidine (Kirkegaard and Perry, TMB 1 Component Stop Solution).

15 Optical densities (OD) are determined spectrophotometrically at 450 nm in a 96-well plate reader (SpectraMax 250, Molecular Devices). Background (no VEGF added) OD values are subtracted from all ODs and percent inhibition is calculated according to the equation:

$$\text{\% Inhibition} = \frac{(\text{OD(VEGF control)} - \text{OD(with test compound)}) \times 100}{\text{OD(VEGF control)} - \text{OD(no VEGF added)}}$$

IC₅₀s are determined on some of the exemplary materials with at least squares analysis program using compound concentration versus percent inhibition.

25 Matrigel® Angiogenesis Model:

Preparation of Matrigel Plugs and *in vivo* Phase: Matrigel® (Collaborative Biomedical Products, Bedford, MA) is a basement membrane extract from a murine
30 tumor composed primarily of laminin, collagen IV and heparan sulfate proteoglycan. It is provided as a sterile liquid at 4°C, but rapidly forms a solid gel at 37°C.

Liquid Matrigel at 4°C is mixed with SK-MEL2 human tumor cells that are transfected with a plasmid containing the murine VEGF gene with a selectable marker. Tumor cells are grown *in vitro* under selection and cells are mixed with cold liquid Matrigel at a ratio of 2×10^6 per 0.5 ml. One half milliliter is implanted subcutaneously near the abdominal midline using a 25 gauge needle. Test compounds are dosed as solutions in Ethanol/Ceremaphor EL/saline (12.5%:12.5%:75%) at 30, 100, and 300 mg/kg po once daily starting on the day of implantation. Mice are euthanized 12 days post-implantation and the Matrigel pellets are harvested for analysis of hemoglobin content.

Hemoglobin Assay: The Matrigel pellets are placed in 4 volumes (w/v) of 4°C Lysis Buffer (20mM Tris pH 7.5, 1mM EGTA, 1mM EDTA, 1% Triton X-100 [EM Science, Gibbstown, N.J.], and complete EDTA-free protease inhibitor cocktail [Mannheim, Germany]), and homogenized at 4°C. homogenates are incubated on ice for 30 minutes with shaking and centrifuged at 14K x g for 30 minutes at 4°C. Supernatants are transferred to chilled microfuge tubes and stored at 4°C for hemoglobin assay.

Mouse hemoglobin (Sigma Chemical Co., St. Louis, MO) is suspended in autoclaved water (BioWhittaker, Inc, Walkersville, MD.) at 5 mg/ml. A standard curve is generated from 500 micrograms/ml to 30 micrograms/ml in Lysis Buffer (see above). Standard curve and lysate samples are added at 5 microliters/well in duplicate to a polystyrene 96-well plate. Using the Sigma Plasma Hemoglobin Kit (Sigma Chemical Co., St. Louis, MO), TMB substrate is reconstituted in 50 mls room temperature acetic acid solution. One hundred microliters of substrate is added to each well, followed by 100 microliters/well of Hydrogen Peroxide Solution at room temperature. The plate is incubated at room temperature for 10 minutes.

Optical densities are determined spectrophotometrically at 600 nm in a 96-well plate reader, SpectraMax 250 Microplate Spectrophotometer System (Molecular Devices, Sunnyvale, CA). Background Lysis Buffer readings are subtracted from all wells.

Total sample hemoglobin content is calculated according to the following equation:

5
$$\text{Total Hemoglobin} = (\text{Sample Lysate Volume}) \times (\text{Hemoglobin Concentration})$$

The average Total Hemoglobin of Matrigel samples without cells is subtracted from each Total Hemoglobin Matrigel sample with cells. Percent inhibition is calculated according to the following equation:

10

$$\% \text{ Inhibition} = \frac{(\text{Average Total Hemoglobin Drug-Treated Tumor Lysates}) \times 100}{(\text{Average Total Hemoglobin Non-Treated Tumore Lysates})}.$$

15 The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

20 From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various conditions and usages.

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WHAT IS CLAIMED IS:

1. A method for treating or preventing a disease in a human or other mammal regulated by tyrosine kinase, (associated with an aberration in the tyrosine kinase signal transduction pathway) comprising administering to a human or other mammal in need thereof a compound of Formula I, a salt form of a compound of Formula I, an isomer of a compound of Formula I or a prodrug of a compound of Formula I

10



I

wherein A is selected from the group consisting of

15

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

20

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

25

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro; and

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(iv) 8 to 10 membered bicyclic heteroaryl group in which the first ring is bonded to the NH of Figure I and contains 1-3 heteroatoms independently selected from the group consisting of O, N, and S, and the second ring is fused to the first ring

using 3 to 4 carbon atoms. The bicyclic heteroaryl group is optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro,

5

B is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of $-L-M$, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

10

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of $-L-M$, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

15

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of $-L-M$, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro; and

20

(iv) 8 to 10 membered bicyclic heteroaryl groups having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of $-L-M$, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro.

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L is selected from the group consisting of:

(a) $-(CH_2)_m-O-(CH_2)_l-$,

(b) $-(CH_2)_m-(CH_2)_l-$,

- (c) $-(\text{CH}_2)_m-\text{C}(\text{O})-(\text{CH}_2)_l-$,
 (d) $-(\text{CH}_2)_m-\text{NR}^3-(\text{CH}_2)_l-$,
 (e) $-(\text{CH}_2)_m-\text{NR}^3\text{C}(\text{O})-(\text{CH}_2)_l-$,
 (f) $-(\text{CH}_2)_m-\text{S}-(\text{CH}_2)_l-$,
 5 (g) $-(\text{CH}_2)_m-\text{C}(\text{O})\text{NR}^3-(\text{CH}_2)_l-$,
 (h) $-(\text{CH}_2)_m-\text{CF}_2-(\text{CH}_2)_l-$,
 (i) $-(\text{CH}_2)_m-\text{CCl}_2-(\text{CH}_2)_l-$,
 (j) $-(\text{CH}_2)_m-\text{CHF}-(\text{CH}_2)_l-$,
 (k) $-(\text{CH}_2)_m-\text{CH}(\text{OH})-(\text{CH}_2)_l-$;
 10 (l) $-(\text{CH}_2)_m-\text{C}\equiv\text{C}-(\text{CH}_2)_l-$;
 (m) $-(\text{CH}_2)_m-\text{C}=\text{C}-(\text{CH}_2)_l-$; and
 (n) a single bond, where m and l are 0.;
 (o) $-(\text{CH}_2)_m-\text{CR}^4\text{R}^5-(\text{CH}_2)_l-$;

wherein the variables m and l are integers independently selected from 0-4,

M is selected from the group consisting of:

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S}(\text{O})_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, $\text{C}(\text{O})\text{R}^1$, $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $\text{NR}^1\text{C}(\text{O})\text{R}^2$, $\text{NR}^1\text{C}(\text{O})\text{OR}^2$, halogen, cyano and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S}(\text{O})_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, $\text{C}(\text{O})\text{R}^1$, $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $\text{NR}^1\text{C}(\text{O})\text{R}^2$, $\text{NR}^1\text{C}(\text{O})\text{OR}^2$, halogen, cyano and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S}(\text{O})_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, $\text{C}(\text{O})\text{R}^1$, $\text{C}(\text{O})\text{OR}^1$, $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $\text{NR}^1\text{C}(\text{O})\text{R}^2$, $\text{NR}^1\text{C}(\text{O})\text{OR}^2$, halogen, cyano and nitro and also oxides (e.g. $=\text{O}$, $-\text{O}^-$ or $-\text{OH}$); and

(iv) 8 to 10 membered bicyclic heteroaryl groups, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro and also oxides (e.g. $=O$, $-O^-$ or $-OH$).

(v) saturated and partially saturated C_3 - C_6 monocyclic carbocyclic moiety optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and, nitro;

(vi) saturated and partially saturated C_8 - C_{10} bicyclic carbocyclic moiety, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(vii) saturated and partially saturated 5 and 6 membered monocyclic heterocyclic moiety, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro, and also oxides (e.g. $=O$, $-O^-$ or $-OH$); and

(viii) saturated and partially saturated 8 to 10 membered bicyclic heterocyclic moiety, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro, and also oxides (e.g. $=O$, $-O^-$ or $-OH$);

wherein each R^1 - R^5 is independently selected from the group consisting of:

- (a) hydrogen,
- (b) C_1 - C_6 alkyl, preferably, C_1 - C_5 linear, branched, or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo;
- (c) phenyl;

(d) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S;

5 (e) C₁-C₃ alkyl-phenyl wherein said alkyl moiety is optionally substituted with halogen up to per-halo; and

(f) C₁-C₃ alkyl-heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said heteroaryl group is a 5-6 membered monocyclic heteroaryl or a 8-10 membered bicyclic heteroaryl, and wherein said alkyl moiety is optionally substituted with halogen up to per-halo,

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wherein each R¹ - R⁵, when not hydrogen is optionally substituted with 1-3 substituents independently selected from the group consisting of C₁-C₅ linear branched or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo, C₁-C₃ alkoxy, wherein said alkoxy is optionally substituted with halogen up to per-halo, hydroxy, amino, C₁-C₃ alkylamino, C₂-C₆ dialkylamino, halogen, cyano, and nitro; and

15

each variable q is independently selected from 0, 1, or 2.

2. A method of claim 1 wherein A, B, and M are each, independently,

20

(i) a substituted or unsubstituted monocyclic heteroaryl group selected from the group consisting of:

2- and 3-furyl, 2- and 3-thienyl, 2- and 4-triazinyl, 1-, 2- and 3-pyrrolyl, 1-, 2-, 4- and 5-imidazolyl, 1-, 3-, 4- and 5-pyrazolyl, 2-, 4- and 5-oxazolyl, 3-, 4- and 5-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 2-, 3- and 4-pyridyl, 2-, 4-, 5- and 6-pyrimidinyl, 1,2,3-triazol-1-, -4- and -5-yl, 1,2,4-triazol-1-, -3- and -5-yl, 1- and 5-tetrazolyl, 1,2,3-oxadiazol-4- and -5-yl, 1,2,4-oxadiazol-3- and -5-yl, 1,3,4-thiadiazol-2- and -5-yl, 1,2,4-oxadiazol-3- and -5-yl, 1,3,4-thiadiazol-2- and -5-yl, 1,3,4-thiadiazol-3- and -5-yl, 1,2,3-thiadiazol-4- and -5-yl, 2-, 3-, 4-, 5- and 6-2H-thiopyranyl, 2-, 3- and 4-4H-thiopyranyl, 3- and 4-pyridazinyl, 2-,3-pyrazinyl,

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30

(ii) a substituted or unsubstituted bicyclic heteroaryl groups selected from the group consisting of:

benzofuryl, benzothienyl, indolyl, benzimidazolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benz-1,3-oxadiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydrobenzofuryl, pyrazolo[3,4-b]pyrimidinyl, purinyl, benzodiazine, pterindinyl, pyrrolo[2,3-b]pyridinyl, pyrazolo[3,4-b]pyridinyl, oxazo[4,5-b]pyridinyl, imidazo[4,5-b]pyridinyl, cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridiazine, cyclohexanopyridazine, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanthiophene and cyclohexanthiophene, or

(iii) a substituted or unsubstituted aryl group without heteroatoms selected from the group consisting of:

phenyl, 1-naphthyl, 2-naphthyl, tetrahydronaphthyl, indanyl, indenyl, benzocyclobutanyl, benzocycloheptanyl and benzocycloheptenyl.

3. A method as in claim 2 wherein the substituents on the groups for A, B, and M are selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *sec*-butyl, and *tert*-butyl, F, Cl, Br, and I.

4. A method of claim 1 wherein the saturated monocyclic and bicyclic carbocyclic moieties are selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and decahydronaphthalene,

the partially saturated monocyclic and bicyclic carbocyclic moieties are selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl and tetrahydronaphthalene,

the saturated monocyclic and bicyclic heterocyclic moieties are selected from the group consisting of include tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolane, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, piperidinonyl, tetrahydropyrimidinonyl, pentamethylene sulfide and tetramethylene sulfide and

the partially saturated monocyclic and bicyclic heterocyclic moieties are selected from the group consisting of dihydropyranyl, dihydrofuranyl, dihydrothienyl, dihydropiperidinyl, and dihydropyrimidinyl.

5 5. A method of claim 1 wherein the structures of A, B and M are each independently selected from the group consisting of optionally substituted phenyl, naphthyl, furyl, isoindolinyl, oxadiazolyl, oxazolyl, isooxazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiadiazolyl, thiazolyl and thienyl.

10

6. A method of claim 5 wherein the substituents of the substituted structures of B are each, independently, selected from the group consisting of methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br and F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino, diethylamino and the structure -L-M.

15

7. A method of claim 5 wherein the substituents of the substituted structures of A and M are each, independently, selected from the group consisting of

20

methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, *tert*-butyl, sec-butyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br and F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino and further include:

25

phenyl, pyridinyl, pyrimidinyl, chlorophenyl, dichlorophenyl, bromophenyl, dibromophenyl, chloropyridinyl, bromopyridinyl, dichloropyridinyl, dibromopyridinyl, methylphenyl, methylpyridinyl, quinolinyl, isoquinolinyl, isoindolinyl, pyrazinyl, pyridazinyl, pyrrolinyl, imidazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, benzopyridinyl, benzothiazolyl,

30

C₁-C₅ acyl;

NH(C₁-C₅ alkyl, phenyl or pyridinyl), such as aminophenyl;

N(C₁-C₅ alkyl)(C₁-C₅ alkyl, phenyl or pyridinyl), such as diethylamino and dimethyl amino;

S(O)_q (C₁-C₅ alkyl); such as methanesulfonyl;

S(O)_q H;

SO₂NH₂;

SO₂NH(C₁-C₅ alkyl);

5 SO₂N(C₁-C₅ alkyl)(C₁-C₅ alkyl);

NHSO₂(C₁-C₅ alkyl); N(C₁-C₃ alkyl) SO₂(C₁-C₅ alkyl);

CO(C₁-C₆ alkyl or phenyl);

C(O)H;

C(O)O(C₁-C₆ alkyl or phenyl), such as C(O)OCH₃, -C(O)OCH₂CH₃, -

10 C(O)OCH₂CH₂CH₃;

C(O)OH;

C(O)NH₂ (carbamoyl);

C(O)NH(C₁-C₆ alkyl or phenyl), such as N-methylethyl carbamoyl, N-methyl carbamoyl, N-ethylcarbamoyl, or N-dimethylamino ethyl carbamoyl;

15 C(O)N(C₁-C₆ alkyl or phenyl)(C₁-C₆ alkyl, phenyl or pyridinyl), such as N-dimethyl carbamoyl;

C(N(C₁-C₅ alkyl)) (C₁-C₅ alkyl);

NHC(O)(C₁-C₆ alkyl or phenyl) and

N(C₁-C₅ alkyl)₂C(O)(C₁-C₅ alkyl).

20 wherein each of the above substituents is optionally partially or fully halogenated.

8. A method as in claim 1 wherein A, B or M of formula I or a combination
25 thereof are independently selected from the group consisting of substituted or unsubstituted phenyl, pyridinyl, naphthyl, quinolinyl and isoquinolinyl.

9. A method as in claim 1 wherein A, B or M of formula I or a combination
30 thereof are independently a phenyl or pyridinyl group, optionally substituted by halogen up to per halo and 0 to 3 times by one or more substituents selected from the group consisting of -CN, C₁-C₅ alkyl, C₁-C₅ alkoxy, -OH, phenyl, up to per halo

substituted C₁-C₅ alkyl, up to per halo substituted C₁-C₅ alkoxy and up to per halo substituted phenyl.

10. A method as in claim 1 wherein A, B and M of formula I follow one of the
5 following combinations:

A= phenyl, B=phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= phenyl, B=pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

10 A=phenyl, B = naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

15 A=pyridinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=isoquinolinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

20 A= isoquinolinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= isoquinolinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

25 A= quinolinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= quinolinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

30 A= quinolinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present.

11. A method as in claim 10 wherein L of formula I is -O-, a single bond, -S-,
-NH-, -N(CH₃)-, -NHCH₂-, -NC₂H₄-, -CH₂-, -C(O)-, -CH(OH)-, -
5 NHC(O)N(CH₃)CH₂-, -N(CH₃)C(O)N(CH₃)CH₂-, -CH₂C(O)N(CH₃)-, -
C(O)N(CH₃)CH₂-, -NHC(O)-, -N(CH₃)C(O)-, -C(O)N(CH₃)-, -C(O)NH-, -CH₂O-, -
CH₂S-, -CH₂N(CH₃)-, -OCH₂-, -CHF-, -CF₂-, -CCl₂-, -S-CH₂-, and -N(CH₃)CH₂-.

10

12. A method as in claim 1 wherein the disease is mediated by the VEGF-
induced signal transduction pathway.

15

13. A method as in claim 12 wherein disease mediated by the VEGF-induced
signal transduction pathway that is treated is characterized by abnormal angiogenesis
or hyperpermeability processes.

20

14. A method as in claim 13 wherein a compound of Formula I, a salt form of
a compound of Formula I, an isolated stereo-isomer of a compound of Formula I or a
prodrug of a compound of Formula I is administered simultaneously with another
angiogenesis inhibiting agent to a patient with such a disorder in the same
formulation or in separate formulations.

25

15. A method as in claim 1 wherein the disease that is treated is one or more
of the following conditions in humans and/or other mammals: tumor growth,
retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related
macular degeneration; rheumatoid arthritis, psoriasis, a bolus disorder associated with
subepidermal blister formation, including bullous pemphigoid, erythema multiforme,
or dermatitis herpetiformis.

30

16. A method as in claim 1 wherein the disease that is treated is one or more of
the following conditions in humans and/or other mammals: tumor growth,

retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis in combination with another condition selected from the group consisting of:

rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) and complications due to total hip replacement.

17. A method as in claim 1 wherein the disease that is treated is one or more of the following conditions in humans and/or other mammals:

tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis,

in combination with an infectious disease selected from the group consisting of:

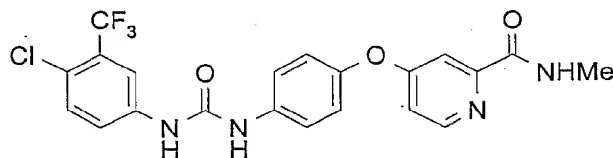
tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enterotoxin A resulting from *Staphylococcus* infection, meningococcal infection, and infections from *Borrelia burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

18. A method as in claim 1, wherein M is substituted by at least one substituent selected from the group consisting of $S(O)_qR^1$, $SO_2NR^1R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, wherein q, R^1 and R^2 are independently as defined in claim 1.

19. A method as in claim 1, wherein M is substituted by at least one substituent selected from the group consisting of $-C(O)R^1$, $C(O)OR^1$, and $C(O)NR^1R^2$, wherein R^1 and R^2 are independently as defined in claim 1.

20. A method of claim 1 wherein M is substituted by $-C(O)NR^1R^2$, wherein R^1 and R^2 are independently as defined in claim 1.

21. A method of treating diseases mediated by the VEGF-induced signal transduction pathway comprising administering the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea of the formula below or a pharmaceutically acceptable salt thereof



22. A method of treating diseases mediated by the VEGF-induced signal transduction pathway comprising administering the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate.

5

23. A method of claim 1 wherein the structures of A, B and M are each, independently selected from the group consisting of phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, naphthyl, substituted naphthyl, isoquinolinyl, substituted isoquinolinyl, quinolinyl and substituted quinolinyl.

10

24. A method as in claim 23, wherein M is substituted by at least one substituent selected from the group consisting of $S(O)_qR^1$, $SO_2NR^1R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$,

15

wherein q, R^1 and R^2 are independently as defined in claim 1.

25. A method of claim 24 wherein M is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1 - C_{10} alkyl, up to per halo substituted C_1 - C_{10} alkyl, -CN, -OH, halogen, C_1 - C_{10} alkoxy and up to per halo substituted C_1 - C_{10} alkoxy.

20

26. A method as in claim 1 wherein L of formula I is -O-, a single bond, -S-, -NH-, -N(CH₃)-, -NHCH₂-, -NC₂H₄-, -CH₂-, -C(O)-, -CH(OH)-, -NHC(O)N(CH₃)CH₂-, -NCH₃C(O)N(CH₃)CH₂-, -CH₂C(O)N(CH₃)-, C(O)N(CH₃)CH₂-, -NHC(O)-, -N(CH₃)C(O)-, -C(O)N(CH₃)-, -C(O)NH-, -CH₂O-, -CH₂S-, -CH₂N(CH₃)-, -OCH₂-, -CHF-, -CF₂-, -CCl₂-, -S-CH₂- or -N(CH₃)CH₂-.

25

27. A method of claim 1 wherein L of formula I is selected from the group consisting of -O-, -S-, -N(R³⁵)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO, where m= 1-3 and R³⁵ is hydrogen, C_1 - C_{10} alkyl, up to per halo substituted C_1 - C_{10} alkyl, -CN, -OH, halogen, C_1 - C_{10} alkoxy or up to per halo substituted C_1 - C_{10} alkoxy.

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28. A method of claim 1 wherein M is substituted by $-C(O)NR^1R^2$ and R^1 and R^2 are as defined in claim 1.

29. A method of claim 1 wherein M is

5 a saturated C_3 - C_6 monocyclic carbocyclic moiety selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, and cyclohexanyl;

a saturated C_8 - C_{10} bicyclic carbocyclic moiety selected from the group consisting of bicyclopentanyl and bicyclohexanyl;

10 a partially saturated C_3 - C_6 monocyclic carbocyclic moiety selected from the group consisting of cyclopentenyl, cyclohexenyl and cyclohexadienyl;

the partially saturated C_8 - C_{10} bicyclic carbocyclic moiety bicyclohexenyl;

15 a substituted naphthyl group selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl and tetrahydronaphthyl; or

20 an 8 to 10 membered bicyclic heteroaryl group selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridiazine, cyclohexanopyridazine, cyclopentanthiophene and cyclohexanthiophene.

30. A method as in claim 12 wherein the disease that is treated or prevented is a KDR-mediated disorder.

25 31. A method as in claim 12 wherein the disease that is treated or prevented is a Flk-1 mediated disorder.

32. A method of regulating *tyrosine kinase* signal transduction comprising administering to a human or other mammal one or more compounds of claim 1.

INTERNATIONAL SEARCH REPORT

Internati Application No

PCT/US 03/04103

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/44 A61K31/4436 A61K31/4725 A61K31/4709 A61K31/17
 A61P35/00 A61P17/06 A61P19/02 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EISENHAUER ET AL.: "Impact of new non-cytotoxics in the treatment of ovarian cancer" INT. J. GYNECOL. CANCER , vol. 11, no. s1, 2001, pages 68-72, XP001062441 page 70, right-hand column -page 71, left-hand column	1-32
X	WO 99 32463 A (BAYER AG) 1 July 1999 (1999-07-01) cited in the application page 6 -page 7 page 15 -page 17	1, 2, 5-9, 12, 13, 15, 16, 23, 26, 27, 30-32

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

6 June 2003

Date of mailing of the international search report

23/06/2003

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INTERNATIONAL SEARCH REPORT

Internet Application No
PCT/US 03/04103

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOTTE S J ET AL: "BAY 43-9006: EARLY CLINICAL DATA IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES" CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, SCHIPHOL, NL, vol. 8, no. 25, 2002, pages 2249-2253, XP001145745 ISSN: 1381-6128 the whole document ---	1-16, 18-27, 29-31
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X	CARTER C A ET AL: "ANTI-TUMOR EFFICACY OF THE ORALLY ACTIVE RAF KINASE INHIBITOR BAY 43-9006 IN HUMAN TUMOR XENOGRAFT MODELS" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 42, no. 923, March 2001 (2001-03), page 923 XP001145482 ISSN: 0197-016X the whole document ---	1-16, 18-27, 29-31
X	WO 99 32455 A (BAYER AG) 1 July 1999 (1999-07-01) cited in the application page 2, line 6 - line 18 page 33 -page 36 ---	1-16, 18-31
X	WO 99 32436 A (BAYER AG) 1 July 1999 (1999-07-01) cited in the application page 2, line 6 - line 18 page 62 -page 74 ---	1-16, 18-31
X	WO 99 32111 A (BAYER AG) 1 July 1999 (1999-07-01) cited in the application page 6, line 22 page 7, line 2 - line 4 page 81 -page 103 ---	1,2,5-9, 12,13, 15,16, 18-20, 26,27, 30,31
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INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/US 03/04103

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 99 32106 A (BAYER AG) 1 July 1999 (1999-07-01) cited in the application</p> <p>page 2, line 1 - line 14 page 80 -page 111</p> <p>---</p>	<p>1,2,5-9, 12,13, 15,16, 18-20, 26,27, 30,31</p>
X	<p>WO 00 41698 A (RIEDL BERND ;LOWINGER TIMOTHY B (JP); DUMAS JACQUES (US); RENICK J) 20 July 2000 (2000-07-20) cited in the application</p> <p>page 7, line 11 page 7, line 24 page 8, line 3 - line 9 page 94 -page 110</p> <p>---</p>	<p>1,2, 5-13, 15-20, 23-27, 30,31</p>
X,P	<p>KUBO KAZUO ET AL: "Synthesis and structure-activity relationship of Quinazoline-Urea derivatives as novel orally active VEGF receptor tyrosine kinase selective inhibitors." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 43, March 2002 (2002-03), page 182 XP001152608 93rd Annual Meeting of the American Association for Cancer Research; San Francisco, California, USA; April 06-10, 2002, March, 2002 ISSN: 0197-016X the whole document</p> <p>---</p>	<p>1-32</p>
X,P	<p>DUMAS J: "Protein kinase inhibitors from the urea class" CURRENT OPINION IN DRUG DISCOVERY AND DEVELOPMENT 2002 UNITED KINGDOM, vol. 5, no. 5, 2002, pages 718-727, XP009011493 ISSN: 1367-6733 the whole document</p> <p>-----</p>	<p>1-32</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/04103

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

 Internat Application No
 PCT/US 03/04103

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
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